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An Expeditious Route to Both Enantiomers of All Carbon Quaternary Stereocenters at C-3 Carbon of Lactams via [3,3]-Sigmatropic Rearrangement: Total Synthesis of (−)-Physostigmine

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Supporting Information

ABSTRACT: A diastereoselective 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. The dependence of the product configuration on the olefin geometry is explained by postulating probable transition states. The success of this method has been shown for the 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 that construct the core of many biologically active alkaloids (**1**−**2**)[1] and pharmaceuticals (**3**−**5**) (Figure 1).[2] Although few attractive chiral auxiliary based

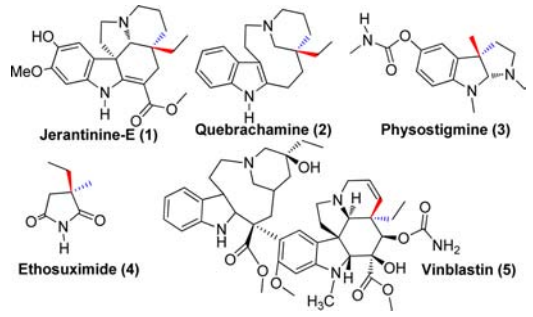

Figure 1. Representative examples containing all carbon quaternary centers at C-3 position of lactams/amines.

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

Due to 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 a 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.

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

We disclose herein the success of our concept as outlined above for preparing lactams of type **7** in high yield (88−97%) and good to excellent diastereoselectivity (*de* = 61−99%). It was also found that the stereochemistry of **7** is dependent both on the olefin geometry and on the configuration of the secondary alcohol **6**, and this advantage is exploited to produce both enantiomers of **7**. Application of this method is also demonstrated by developing an efficient total synthesis of (−)-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 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[11] of **9** with -OTBS protected L-lactaldehyde (**10**).[12] 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

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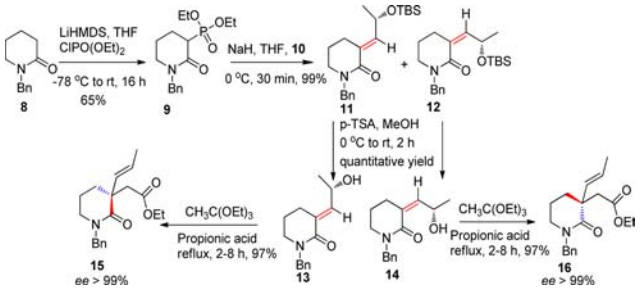
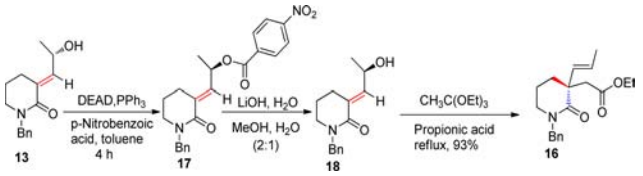
Scheme 2. [3,3]-Sigmatropic Shift of 13 and 14



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)[13,14] which gave **15** in 97% isolated yield and >99% enantiomeric purity (determined by chiral-phase HPLC analysis, Chiralcel OD-H, *iso*-propanol/*n*-hexane; 10:90).[15] Under the same reaction conditions, however, **14** produced a 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 Mitsunobu's reaction[16] followed by ester hydrolysis using LiOH, H_2O (Scheme 3). The resultant **18** on usual rearrangement

Scheme 3. [3,3]-Sigmatropic Shift to All Carbon Quaternary Stereocenters of Piperidinone Ring System Using 18



produced **16** in 93% yield (*ee* = 97%).[17] 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. 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**, the suprafacial approach of the incoming $-CH_2CO_2Et$ group makes the C3−C2 bond above the plane leading to the formation of **15**, whereas **16** is formed by involving

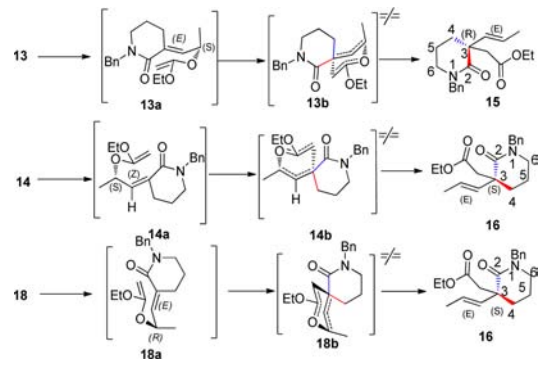
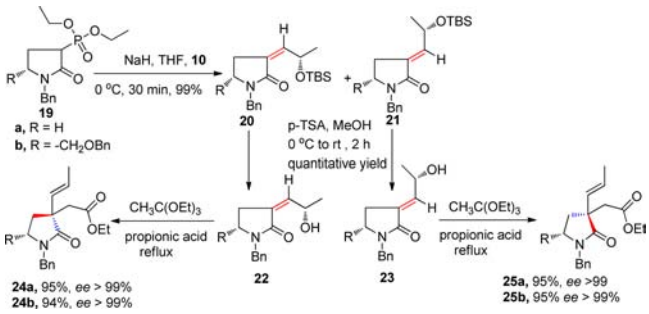


Figure 2. Transition state for [3,3]-sigmatropic rearrangement.

14b, where owing to the *Z*-geometry of the olefinic bond, the C3−C4 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 the C3−C2 bond below the plane for the formation of **16**.

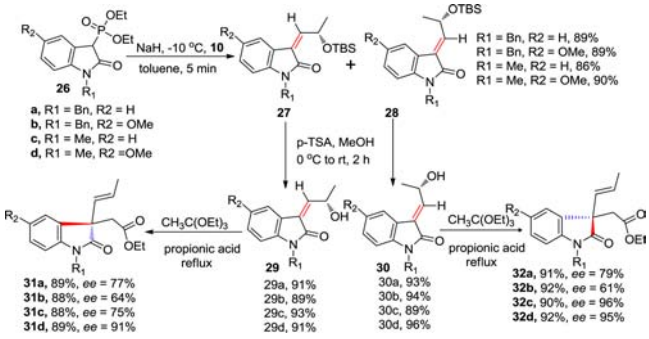
With this interesting result in hand, we explored this strategy further with the pyrrolidinone derivatives **22** and **23** as well by following the identical experimental conditions as discussed above and obtained corresponding 3,3-dialkylated derivatives **24** and **25** as shown in Scheme 4.

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 as 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 comprising a large number of biologically active natural products and pharmaceutically active agents.[18] Although there are several interesting approaches known for the construction of enantiomerically pure 3,3-disubstituted oxindoles,[19−28] developing another conceptually new strategy, as shown in Scheme 5, would enhance the

Scheme 5. [3,3]-Sigmatropic Rearrangements of Oxindole Derivatives 31−32



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 corresponding −OTBS deprotected **29a** as well as **30a** produced **31a** (*ee* = 77%) and **32a** (*ee* = 79%),[15] 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

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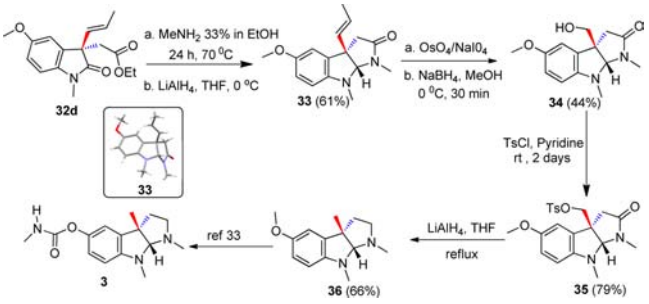
which ascertained that isomerization of the olefinic double bond does happen both in the presence of room light and with propionic acid.[29] The generality of this rearrangement was also established by studying various other substrates (**29b−29d** and **30b−30d**) as shown in Scheme 5.

Physostigmine (**3**), isolated from the *Physostigma venenosum*,[30] is a clinically used molecule for treatment glaucoma and myasthenia gravis and also is a therapeutic agent for Alzheimer's disease.[31] Owing to interesting biological activities associated with this molecule, the attention of many synthetic chemists is drawn toward its asymmetric synthesis.[32] Due to realizing the fact that we have an interesting strategy for constructing structural frameworks of type **31** and **32** easily, we were motivated to employ our strategy for the synthesis of **3** (Scheme 6). In this context, **33** was prepared in 61% yield by the reaction

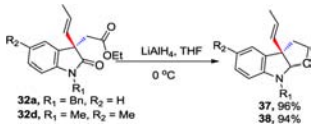
Scheme 6. Total Synthesis of (−)-Physostigmine



of **32d** with ethanolic methylamine followed by $LiAlH_4$ reduction which on recrystallization using ethyl acetate/hexane gave optically pure **33** (Kromasil 100-5C8, ACN/H_2O; 58:42, retention time 3.59 min, *de* = >99%) whose absolute configuration was confirmed by X-ray crystal structure analysis.[33,34] The oxidative cleavage of the olefinic double bond of **33** using $OsO_4/NaIO_4$ produced the corresponding aldehyde which upon reduction with $NaBH_4$ in methanol gave **34** in 45% yield. Tosylation (TsCl, pyridine) of **34** followed by reduction with LAH in refluxing THF produced (−)-esermethole (**36**, 66%) which was transformed to **3** using previously reported protocols.[35] After synthesizing **3** successfully from **32d**, it was also visualized that a 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.[36]

Thus, reduction of **32a** and **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.

Scheme 7. Synthesis of Furanoindolines



In conclusion, we have developed a conceptually new route for the construction of diastereomerically enriched 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 in 11 linear steps and 4.5% overall yield from commercially available starting material. Further exploration of this method in the synthesis of other biologically active alkaloids is in progress.

■ ASSOCIATED CONTENT

Supporting Information

Details of the experimental procedure, characterization data for all new compounds, crystallographic data in CIF. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) For details of optimization study, please see Supporting Information.
(14) Compound **13** was successfully converted to **15** at 10.5 g scale without affecting the yield and enantiomeric excess.
(15) Please see Supporting Information for the preparation of the corresponding racemic compound.
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