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seco-C/D Ring Analogues of Ergot Alkaloids. Synthesis via Intramolecular Heck and Ring-Closing Metathesis Reactions

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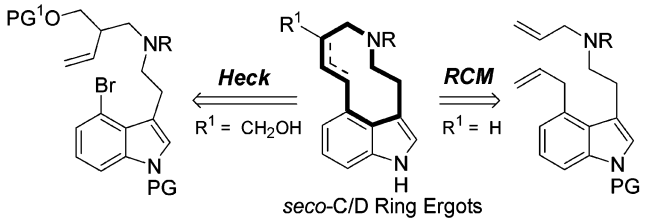
ABSTRACT



Intramolecular Heck and ring-closing metathesis reactions on key intermediates 10 and 15, respectively, provide efficient entries into *seco*-C/D ring analogues of Ergot alkaloids 12 and 16, compounds of potential synthetic and biological interest.

We report on the construction of compounds **12** and **16**, comprising *seco*-C/D ring Ergot alkaloid analogues using key Heck[1] and ring-closing metathesis (RCM)[2] reactions. The Ergots represent a significant class of indole alkaloids of broad pharmacological activity.[3] Historically, Ergot alkaloids were among the first used drugs for the treatment of migraine (ergotamine tartrate, 1920s, and dihydroergotamine mesylate, 1950s)[4] and today, despite the advent of selective 5-HT receptor inhibitors (sumatriptan[5] and others[6]), methysergide continues to be used as an antimigraine prescription drug (Figure 1).[7]

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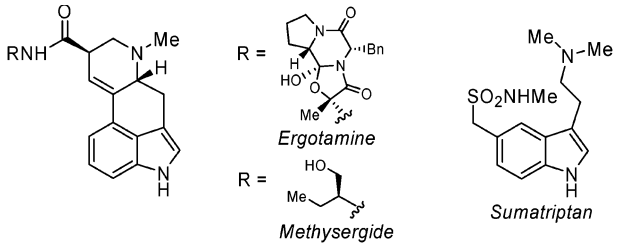


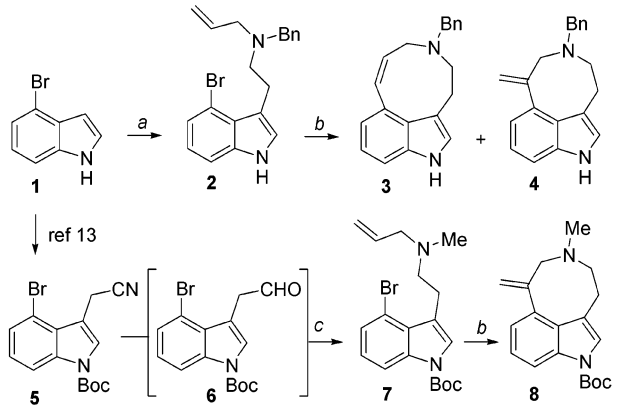
Figure 1.

Consequently, the search for receptor-selective Ergot analogues continues to be the subject of intense synthetic activity.[8]

Our work provides new entries into indole 3,4-fused macrocycles **12** and **16**, representing the *seco*-C/D ring analogue of the naturally occurring lysergol (Scheme 2), and offers new structural types as further probes of 5-HT receptor inhibitor activity.[9]

Model reactions (Scheme 1) were investigated as a prelude to the Heck macrocyclization **10** → **11**. Initiated from

Scheme 1[a]



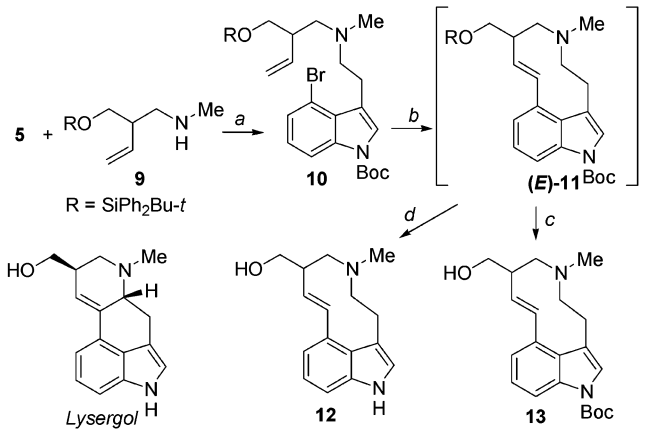
[a] Reaction conditions: (*a*) $POCl_3$, DMF, 0 to 40 °C (1 h) (78%); then $MeNO_2$, cat. NH_4OAc, reflux, 3 h (80%); then $LiAlH_4$, THF, reflux, 4 h (88%); then PhCHO, $NaBH(OAc)_3$, DCM−THF, rt (46%); then AllylBr, MeCN, rt, 24 h (69−72%). (*b*) 25 mol % $Pd(OAc)_2$, 55 mol % P(*o*-Tol)$_3$, NEt_3, MeCN, reflux, 12 h (**3**, 24%; **4**, 21%; **8**, 30%). (*c*) DIBALH, 0 °C (15 min) to rt (2 h), DCM; then AllylNHMe, $NaBH(OAc)_3$, DCM, rt (overnight) (38%).

4-bromoindole (**1**),[10] two routes toward the required tryptamines **2** and **7** have been compared for efficiency. In the first route, sequential Vilsmeier−Haack, Henry nitroaldol condensation,[11] reduction with $LiAlH_4$, reductive amination of the formed tryptamine [PhCHO/$NaBH(OAc)_3$],[12] and allylation provided the indole **2** (18% yield over five steps). The main drawback of this route is the formation of *N*,*N*-dibenzylated 4-bromotryptamine (up to 24% yield) during the reductive amination step. Alternatively, cyanomethylation of **1** and *N*-Boc protection[13] gave **5**, which was partially reduced with DIBALH[13,14] to the intermediate indolylacetaldehyde **6**; the latter, without isolation, was subjected to reductive amination[12] with *N*-allyl-*N*-methylamine providing **7** in 23% overall yield.

The reaction of **2** with $Pd(OAc)_2$ (25 mol %) and P(*o*-Tol)$_3$ (55 mol %) in refluxing MeCN (*c* 0.01 M) containing 2.5 equiv of NEt_3 was complete within 12 h to afford 9-*endo*-**3** and 8-*exo*-**4** products in 24 and 21% yields, respectively. In contrast, subjection of **7** to the same reaction conditions led to 8-*exo*-**8** in 30% yield as the only isolable product. While it is premature to interpret the observed regioselectivity of cyclization of **2** *vs* **7** as a function of difference in N-substituents, these results are consistent with the observations of Roberts *et al.* on the cyclization of a carbocyclic analogue.[15] Despite this poor selectivity, we proceeded to examine the 10-membered ring cyclization based on the generalization that *endo*-cyclization predominates with increasing chain length.[1e]

Thus, the synthesis of the *seco* C/D-ring analogue (**11**) was undertaken by rapid assembly of the Heck precursor **10** (48% yield) through reductive amination of **6** with homoallylic amine **9**[16] (Scheme 2). Unfortunately, direct adoption

Scheme 2[a]



[a] Reaction conditions: (*a*) DIBALH, 0 °C (4 h) to rt (1 h), DCM, then **9**, $NaBH(OAc)_3$, 0 °C to rt (overnight), DCM (48%). (*b*) 30 mol % $Pd(OAc)_2$, 90 mol % P(*o*-Tol)$_3$, DBU, Tol, 110 °C, 3−3.5 days, or 35 mol % $Pd(OAc)_2$, 105 mol % P(*o*-Tol)$_3$, DBU, Xylenes, 142 °C, 9 h. (*c*) TBAF, THF, rt, 1 h (32% from **10**). (*d*) 3 N HCl, MeOH, reflux, 8 h (41% from **10**).

of the conditions used for the conversion of **2** and **7** led to an intractable mixture of products. After extensive screening of conditions, it was found that conducting the reaction in refluxing toluene for prolonged times (up to 3 days) with DBU as a base provided a ∼3:1 mixture of the *trans*-macrocycle (*E*)-**11** with a minor product assigned as a *cis*

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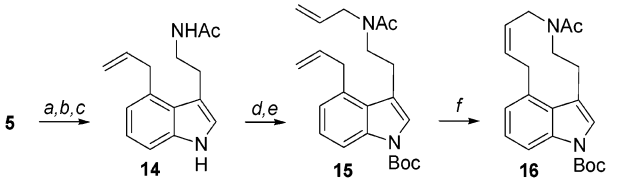
isomer (confirmed from ^{1}H NMR and LC-MS analysis).[16,17] Replacement of the reaction solvent to xylenes allowed the reaction time to be shortened to 9 h without affecting the above ratio of products. Difficulty in separation of isomers forced conversion of **11** into *seco*-C/D ring lysergol **12** and its *N*-Boc derivative **13**. Accordingly, treatment of the crude Heck reaction mixture with HCl or TBAF afforded pure **12** and **13** in 32 and 41% yields from **10**, respectively.

To test the RCM protocol[2] for the construction of the *seco*-C/D ring framework **16**, the common starting 4-bromoindole **5** was subjected to sequential Stille coupling with allyltributyltin,[18] LAH reduction, and acylation to furnish the 4-allyltryptamine **14** in 42% overall yield (Scheme 3). Treatment

Scheme 3[a]



[a] Reaction conditions: (*a*) $AllylSnBu_3$, 5 mol % $Pd(PPh_3)_4$, Tol, 110 °C, 14 h (69%). (*b*) $LiAlH_4$, E_2O-THF, rt, 12 h (61%). (*c*) Ac_2O, Py, rt, 20 h (97%). (*d*) Boc_2O, NEt_3, cat. DMAP, DCM, rt, 2 h (73%). (*e*) *n*-BuLi, AllylBr, THF, −78 °C (5 min) to rt (20 h) (65%). (*f*) 30 mol % $(PCy_3)_2(Cl)_2Ru{=}CHPh$, DCM (*c* 0.0021 M), 40 °C, 20 h (69%).

with Boc_2O followed by *N*-allylation afforded the RCM precursor **15**. Using the first-generation catalyst [$(PCy_3)_2(Cl)_2$-Ru=CHPh][2] in refluxing CH_2Cl_2 under syringe pump addition of substrate and two loadings of catalyst[19] afforded smooth reaction to give **16** as a single (*Z*)-isomer (^3J = 10.4 Hz) in 69% yield.

In summary, the intramolecular Heck reaction has been probed in context of *8*- (**4**, **8**) *vs 9*-membered (**3**) ring formation and applied to the construction of the macrocyclic analogue **12** of lysergol. In addition, and more efficiently, macrocycle **16**, representing the first *seco*-C/D ring ergot alkaloid core, has been prepared by RCM.[20] Extension of this rational methodology for the synthesis of other *seco*-ergolines and related systems for bioactivity studies and the transformation of prototypes **10** and **15** into the ergot alkaloids may be anticipated.

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Supporting Information Available: Experimental details and data of intermediate and final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For full experimental details, see Supporting Information.

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