

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

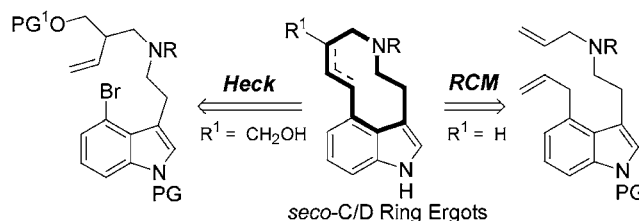
Alexey V. Kalinin,[†] Brian A. Chauder,^{‡,§} Suman Rakhit,[‡] and Victor Snieckus^{*,†}

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1; Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6; MCR Research, Inc., York University, 4700 Keele Street, Toronto, Ontario, Canada M3J 1P3

snieckus@chem.queensu.ca

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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 Heck¹ 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 (sumatriptan⁵ and others⁶), methysergide continues to be used as an antimigraine prescription drug (Figure 1).⁷

[†] University of Waterloo.

[‡] Queen's University.

[§] Present address: GlaxoSmithKline Research & Development, Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709-3398.

[‡] MCR Research, Inc.

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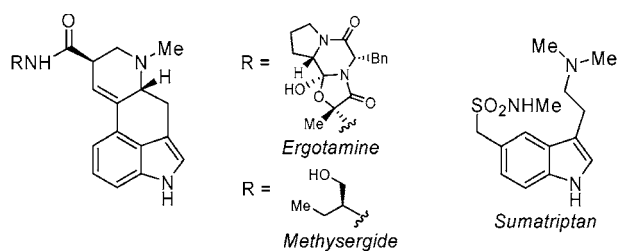
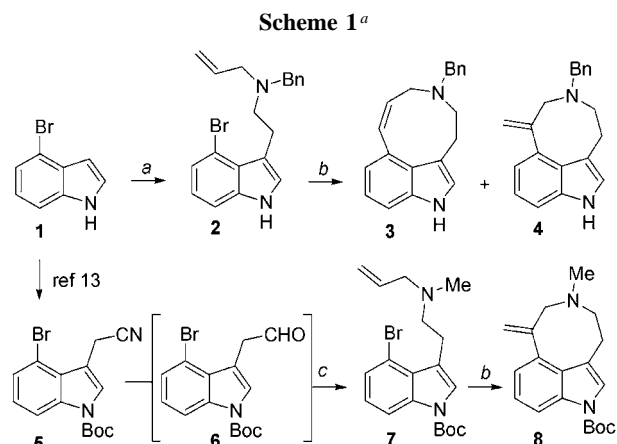


Figure 1.

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



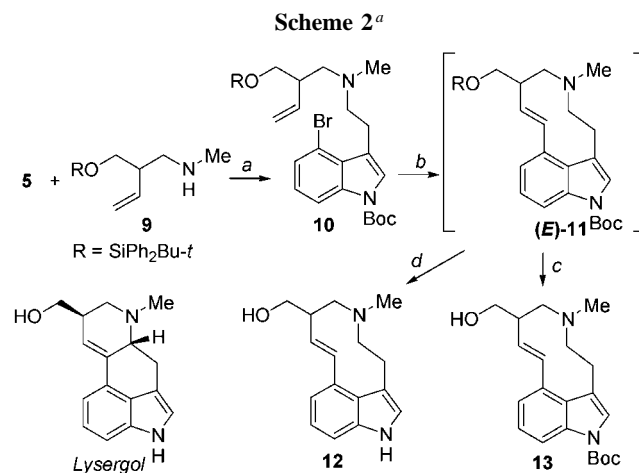
^a Reaction conditions: (a) POCl₃, DMF, 0 to 40 °C (1 h) (78%); then MeNO₂, cat. NH₄OAc, reflux, 3 h (80%); then LiAlH₄, THF, reflux, 4 h (88%); then PhCHO, NaBH(OAc)₃, DCM-THF, rt (46%); then AllylBr, MeCN, rt, 24 h (69–72%). (b) 25 mol % Pd(OAc)₂, 55 mol % P(*o*-Tol)₃, NEt₃, MeCN, reflux, 12 h (**3**, 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 LiAlH₄, 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 protection¹³ gave **5**, which was partially reduced with DIBALH^{13,14} to the intermediate indolylacetaldehyde **6**; the latter, without isolation, was subjected to reductive amination¹² 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 NEt₃ was complete within 12 h to afford 9-*endo*-**3** and 8-*exo*-**4** products in 24 and 21% yields, respectively. In contrast, subjecting 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.¹⁶

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



^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**).

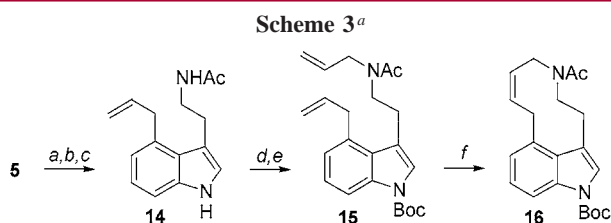
of the conditions used for the conversion of **2** and **7** led to an intractable mixture of products. After extensive screening of conditions, it was found that conducting the reaction in refluxing toluene for prolonged times (up to 3 days) with DBU as a base provided a ~3:1 mixture of the *trans*-macrocycle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

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isomer (confirmed from ^1H 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 protocol² 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



^a Reaction conditions: (a) AllylSnBu_3 , 5 mol % $\text{Pd}(\text{PPh}_3)_4$, Tol, 110 °C, 14 h (69%). (b) LiAlH_4 , Et_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 % $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}$, 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 $[(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}]^2$

in refluxing CH_2Cl_2 under syringe pump addition of substrate and two loadings of catalyst¹⁹ 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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