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Novel entry to the *Ergot* alkaloids via ring closing metathesis

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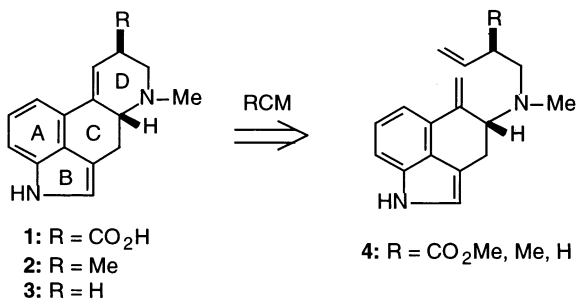
Abstract—A novel entry the *Ergot* alkaloids has been developed. It features a Heck reaction followed by hydride capture to generate the key tricyclic intermediate **12** and a ring closing metathesis reaction to give the tetracyclic ergoline ring system **3**.

The development of new and general strategies for the synthesis of biologically important natural and unnatural substances constitutes an area of considerable interest in organic chemistry. In this context, we were attracted some years ago to the potential of using ring closing metathesis (RCM) reactions as key constructions for alkaloid synthesis.[1,2] We have recently reported the application of such reactions to the syntheses of manzamine A and FR900482.[3,4] As part of an ongoing program in developing the utility of RCM reactions, we were intrigued by the possibility of exploiting such a construction in formulating a novel synthetic approach to the tetracyclic *Ergot* alkaloids lysergic acid (**1**) and lysergine (**2**) via cyclization of a precursor diene such as **4** (R = CO_2Me, Me) (Scheme 1).[5] We now report the successful completion of some preliminary studies that establish the underlying viability of a novel entry to the *Ergot* alkaloids as manifested in the synthesis of the C(8) unsubstituted ergoline derivative **3**.

The basic strategy that emerged for preparing **3** was designed to be adaptable so it could be modified in a straightforward fashion for the asymmetric syntheses of the natural *Ergot* alkaloids, including lysergic acid (**1**) and lysergine (**2**). The known dehydrotryptophan **7** was readily prepared by palladium-mediated coupling of the *N*-tosyl derivative of 4-bromoindole **6** with a protected dehydroalanine in 56% overall yield from **5** (Scheme 2).[6,7] *N*-Methylation of **7** followed by hydrogenation of the dehydroamino acid moiety of **8** with Wilkinson's catalyst under 100 psi hydrogen proceeded efficiently, albeit slowly, to give the bromotryptophan **9** in about 88% yield. If 10% Pd/C was used as the catalyst, complete hydrogenolysis of the aryl bromide occurred. Although the present route provides **9** as a racemate, it should be possible to modify the synthetic plan to prepare **9** or closely related analogs in an enantiomerically pure form.[8]

Developing the tactics for converting **9** into the key tricyclic intermediate **12** required considerable experimentation. The first plan was to induce radical cyclization of the bromo acetylene **10** into **12** via a 6-*exo*-*dig* closure. Toward this end, reduction of the ester **9** with DIBAL-H furnished an intermediate aldehyde that was transformed directly into the acetylene **10** using 1-diazo-(2-oxopropyl)phosphonate (73% overall yield from **9**).[9] However, several preliminary attempts to effect radical cyclization of **10** (Bu_3SnH, cat. AIBN, toluene, Δ) afforded only the corresponding debrominated product. Placement of a trimethylsilyl group on terminal acetylenes has been reported to facilitate radical cyclizations and to enhance the *exo*/*endo* selectivity,[10] but when **11** was treated with (Bu_3SnH in the presence of AIBN, only traces of cyclized product were detected in the reaction mixture.



1: R = CO_2H
2: R = Me
3: R = H

4: R = CO_2Me, Me, H

Scheme 1.

Keywords: ring closing metathesis; Heck reaction; organometallic; amino acid.

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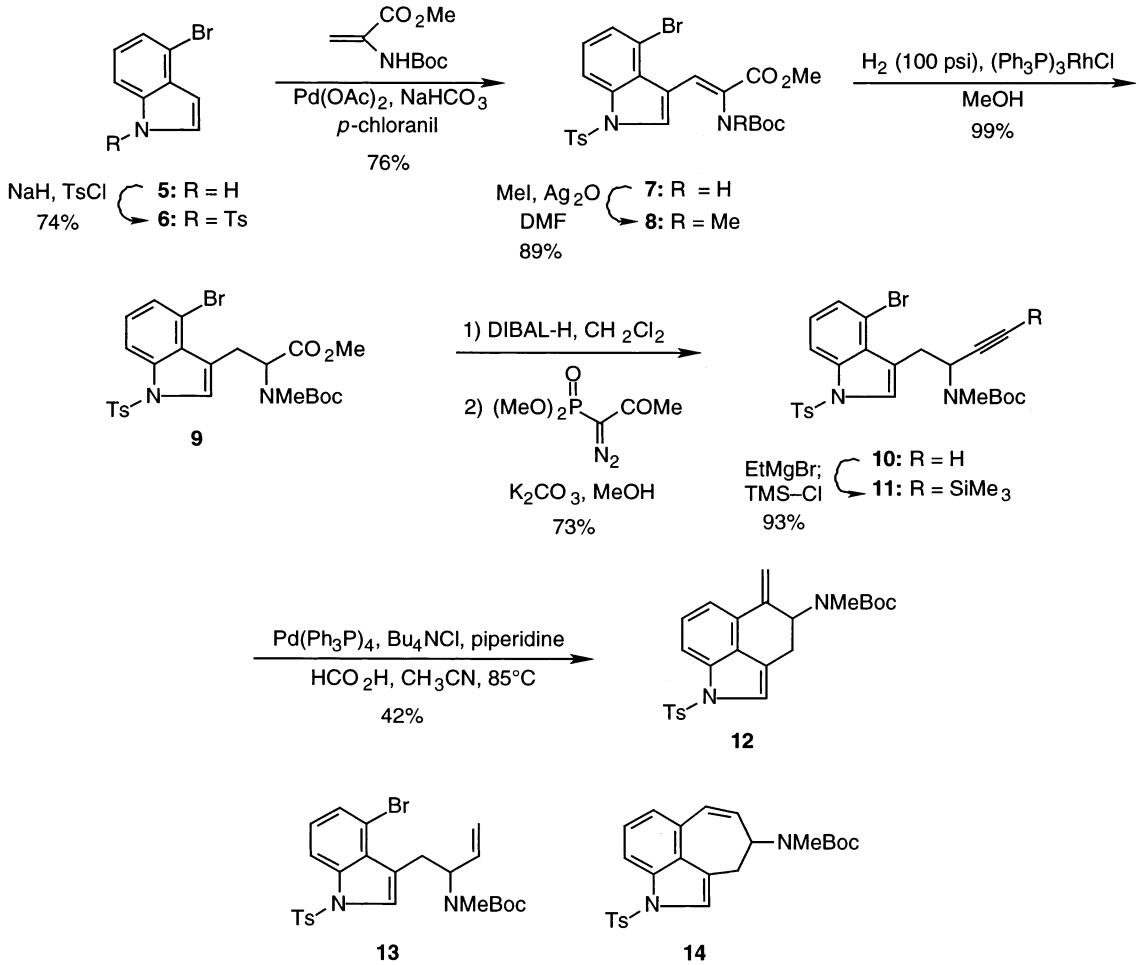


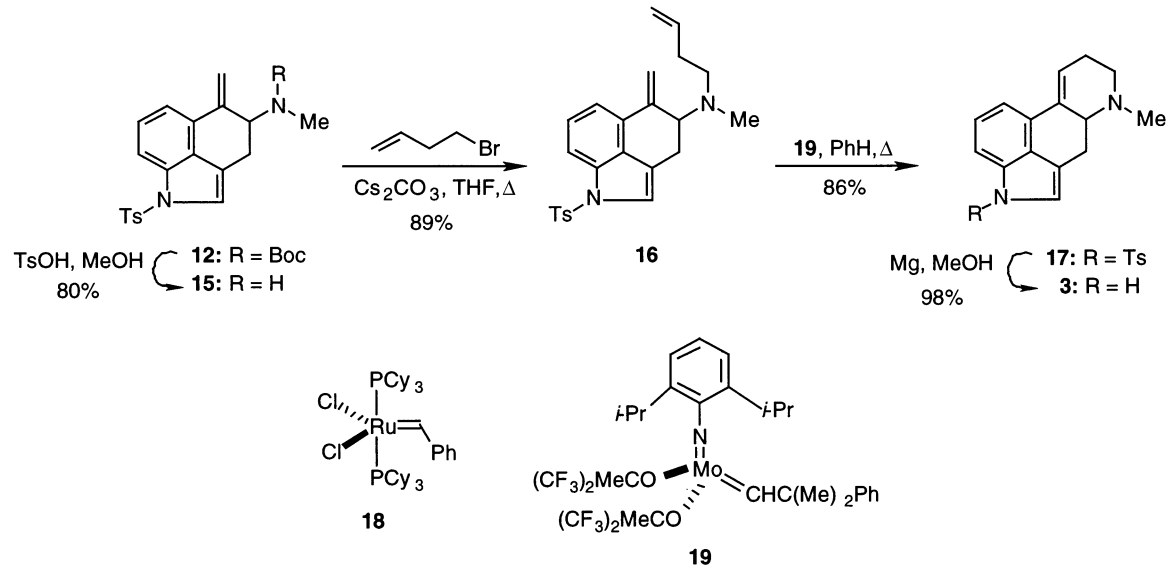
Scheme 2.

These results did not bode well for preparing **12** by a radical cyclization, so other options were considered, and an intramolecular Heck cyclization emerged as an attractive alternative. The requisite alkene **13** was readily prepared from **9** by sequential DIBAL-H reduction followed by Wittig olefination. However, subjecting **13** to typical Heck conditions [$Pd(OAc)_2$, $(o\text{-tol})_3P$, Bu_4NCl, Et_3N, MeCN, Δ) afforded the undesired seven-membered ring product **14** in 65% yield. Subsequent examination of models suggested that the 7-*endo* mode of cyclization allowed more facile attainment of an eclipsed relationship between the aryl carbon–palladium bond, which was formed by oxidative addition, and the reacting carbon–carbon double bond, an arrangement Overman found to favor Heck cyclization.[11] It then occurred to us that one way to disfavor the 7-*endo* cyclization pathway would be to replace the terminal olefin in **13** with an alkyne moiety, which could not adopt an eclipsed relationship with the aryl carbon–palladium bond. The accessible twisted orientation between the alkyne and the carbon–palladium bond might then kinetically favor formation of a six-membered ring. After considerable experimentation, we discovered that **10** could be selectively converted into **12** in reasonable yield by a Heck reaction followed by hydride capture.[12] Use of other palladium catalysts, bases, and additives led to the formation of **14** as a significant and inseparable by-product.

With quantities of **12** in hand, the stage was set to examine the key ring closing metathesis. In this context it is noteworthy that there are few examples of RCM reactions involving exocyclic olefins and phenyl substituted alkenes, so success was clearly not assured.[13,14] Removal of the Boc protecting group from **12** followed by *N*-alkylation of the amine **15** thus obtained with 4-bromo-1-butene gave **16** in 71% overall yield (Scheme 3).[15]

When **16** was heated with the Grubbs catalyst **18**, only small quantities of **17** were formed; however, the RCM of **16** to give **17** using the more reactive Schrock catalyst **19** proceeded in 86% yield. Removal of the tosyl protecting group then delivered the desired ergoline **3** in nearly quantitative yield.

These results further demonstrate the utility of RCM reactions to elaborate the ring systems found in complex alkaloid natural products. Further applications of such processes are under active investigation, and the results of these studies will be reported in due course.



Scheme 3.

Acknowledgements

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15. Spectral data for selected compounds: **12**, ^{1}H NMR (DMSO-d_6, 353 K): δ 7.80–7.78 (d, J=8.4 Hz, 2H), 7.73 (d, J=8.1 Hz, 1H), 7.49 (d, J=8.5 Hz, 1H), 7.42 (d, J=0.9 Hz, 1H), 7.36–7.30 (comp, 3H), 5.86 (d, J=2.1 Hz, 1H), 5.04 (d, J=2.1 Hz, 1H), 4.96–4.91 (m, 1H), 3.09–2.98 (comp, 2H), 2.76 (s, 3H), 2.31 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (DMSO-d_6, 353 K): δ 154.6, 144.7, 138.4, 134.4, 132.8, 129.7, 128.8, 127.6, 126.0, 125.5, 120.1, 117.4, 116.8, 112.1, 109.0, 78.7, 55.3, 29.8, 27.7, 24.7, 20.5; **16**, ^{1}H NMR ($CDCl_3$): δ 7.76–7.70 (comp, 3H), 7.34–7.16 (comp, 5H), 5.75–5.62 (m, 1H), 5.73 (s, 1H), 5.36 (s, 1H), 5.00–4.89 (comp, 2H), 3.58 (app t, J=5.8 Hz, 1H), 2.97 (app d, J=5.8 Hz, 2H), 2.58–2.44 (comp, 2H), 2.31 (s, 3H), 2.22 (s, 3H), 2.19–2.12 (comp, 2H). ^{13}C NMR ($CDCl_3$): δ 144.5, 141.4, 136.8, 135.8, 133.7, 130.4, 129.7, 129.2, 126.7, 125.7, 119.8, 118.9, 117.0, 115.3,

112.3, 64.3, 53.8, 38.4, 31.9, 29.7, 23.4, 21.5; **17**. ^{1}H NMR ($CDCl_3$): δ 7.74–7.71 (comp, 3H), 7.28–7.17 (comp, 5H), 6.46–6.44 (m, 1H), 3.51 (dd, $J=15.1$, 5.3 Hz, 1H), 3.09–3.02 (m, 1H), 2.97–2.95 (m, 1H), 2.61–2.51 (comp, 3H), 2.52 (s, 3H), 2.31 (s, 3H), 2.22–2.17 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 144.7, 135.6, 133.5, 133.0, 129.8, 129.7, 128.3, 126.7, 125.8, 122.4, 119.8, 117.9, 116.2, 112.1, 62.1, 52.3, 43.7, 26.7, 25.7, 21.5.