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Synthesis of the Western Half of the Lolicines and Lolitrems

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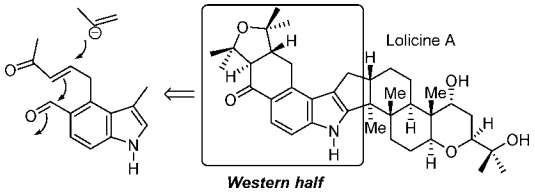
ABSTRACT



The synthesis of the highly substituted indole portion of the complex tremorgenic natural products lolicine A and B is presented. The Diels−Alder reaction of a quinone monoimine enables the synthesis of an appropriately substituted indole. The key step in the synthesis is a tandem isopropenyl cuprate addition/aldol cyclocondensation which provides the necessary functionality for elaboration to the 2,2,5,5-tetramethyltetrahydrofuran.

Neotyphodium-type fungi contaminate many of the world's agriculturally important ryegrasses and are implicated in the toxicity of such grasses.[1] These toxic ryegrasses are indigenous to every continent with the exception of Antarctica and contribute to a disorder known as perennial ryegrass staggers, a neurotoxic affliction causing the grazing livestock to exhibit tremors.[2] The lolicines, lolitrems, and lolitriols (isolated from *Neotyphodium lolii*)[3] and the related penitrems (from *Penicillium cyclopium* and *Penicillium crustosum*)[4] are known as tremorgenic indole terpenoids (Figure 1). Although other tremorgenic indoles with similar "eastern halves" exist, the lolicines, lolitrems, and penitrems are privileged in their possession of a cyclohexane fused to the 4,5 position of the indole moiety. A notable and unique feature of the lolicines and lolitrems is the presence of a 2,2,5,5-tetramethyltetrahydrofuran ring cis or trans fused (C31−C35) to the α,β-carbons of a tetralone.

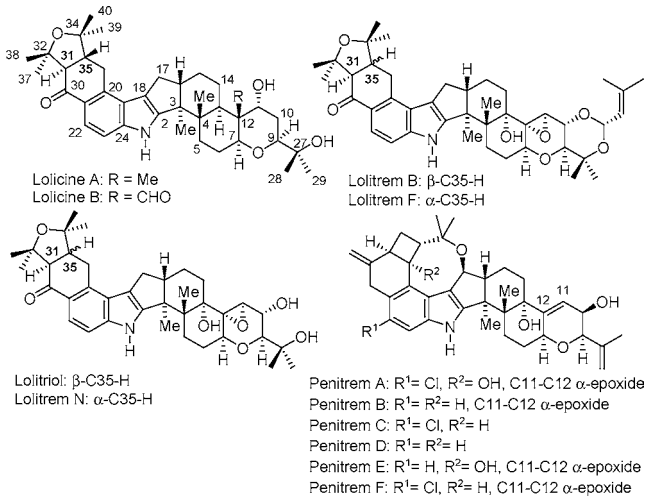


Figure 1. Selected tremorgenic indole natural products.

These tremorgens, aside from their biological interest, represent new, complex architectures for assembly by total

(1) White, J. F., Jr. *Plant Dis*. **1987**, *71*, 340−342.
(2) Neill, J. C. *N. Z. J. Sci. Technol*. **1941**, *23*, 185A−193A.
(3) (a) Munday-Finch, S. C.; Wilkins, A. L.; Miles, C. O. *J. Agric. Food Chem.* **1998**, *46*, 590−598. (b) Munday-Finch, S. C.; Wilkins, A. L.; Miles, C. O. *J. Agric. Food Chem.* **1996**, *44*, 2782−2788.
(4) (a) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77−78. (b) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289−291. (c) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1847−1856.

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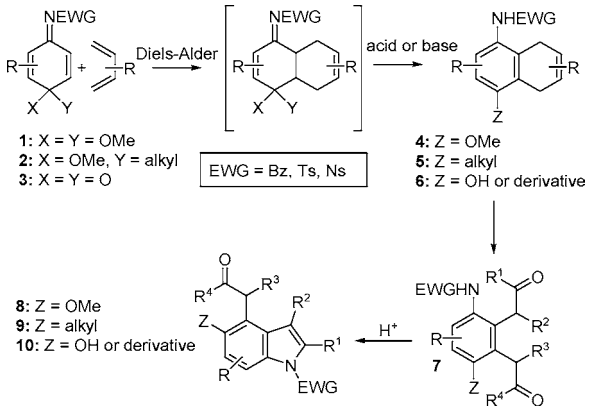
synthesis. Indeed, Smith and co-workers have been successful in preparing the formidable penitrem D.[5] Curran and co-workers have also put forth an inventive approach to a tricyclic substructure of the penitrems containing the cyclobutane moiety.[6] There has only been one brief study nominally directed toward the lolicine-type structure.[7] Herein, we report a successful construction of the western half of the lolicines/lolitrems.

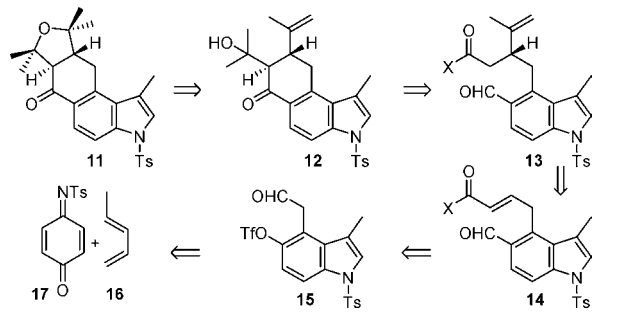
Recently, we reported that highly substituted indoles (e.g., **8**−**10**) could be rapidly assembled by the oxidative cleavage of amino dihydronaphthalenes[8] **4**−**6** which are prepared via the Diels−Alder reaction of quinoid imines **1**−**3** (Scheme 1).[9] This indole preparation strategy addresses the longstanding challenge facing indole chemists, namely, a flexible preparation of indoles bearing complex substitution on the benzenoid portion of the molecule.

Scheme 1. General Synthesis of Complex Indoles



Scheme 2 shows a brief retrosynthesis of a western half model of the lolicines. The 2,2,5,5-tetramethyltetrahydrofuran of the target **11** would be prepared from **12** by acid-catalyzed ring closure of a tertiary alcohol onto an isopropenyl moiety. The tetralone system in **12** would arise from an aldol-type ring closure via **13** which in turn would be prepared via conjugate addition of an isopropenyl nucleophile to a substrate such as **14**. The required 5-formyl moiety in **14** would be installed via the aryl triflate in **15**, whereas the

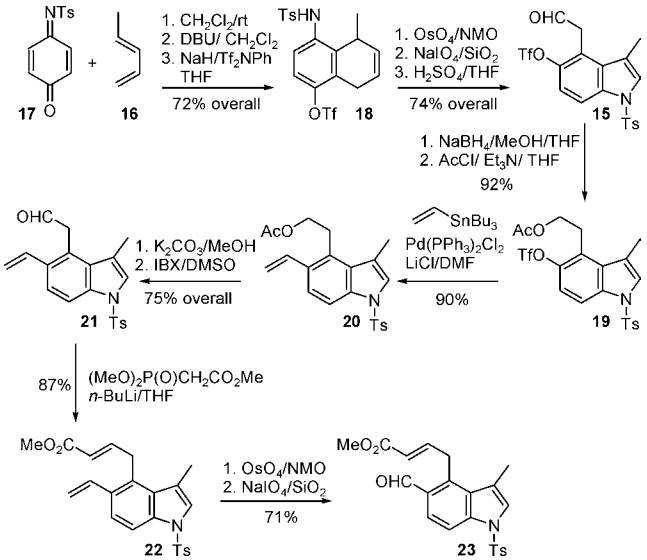
Scheme 2. Retrosynthesis for a Lolicine Western Half Model



Michael acceptor in **14** would be available via Horner−Emmons elaboration of the aldehyde group present in **15**. The synthesis of indole **15** has been reported by us[7a] and arises via the strategy in Scheme 1 from dienophile **17** and *trans*-piperylene **16**.

Our synthetic efforts commenced (Scheme 3) with the cycloaddition of quinone monoimine **17** with *trans*-piperylene to yield the expected cycloadduct which was treated with DBU to effect aromatization (vide supra, Scheme 1). The phenolic moiety was triflated to yield **18** in 72% yield over three steps from **17**. Conversion of the dihydronaphthalene **18** to indole **15** was done in the usual manner in 74% overall yield by oxidative cleavage of the double bond and treatment with acid. It was necessary to protect the resulting aldehyde in **15** because it interfered (in an as yet unknown way) with upcoming cross-coupling chemistry. Although this could be done via ketalization, reduction and acetate formation to give **19** were both more convenient and higher yielding (92%). After exhaustive attempts at direct formylation of **19**, we decided to use a vinyl group as a latent aldehyde. To this end, Stille coupling proceeded in excellent yield (90%) to produce styrene **20**. Upon reflection, this was

Scheme 3. Elaboration of the Indole



(5) (a) Kanoh, N.; Smith, A. B., III.; Ishiyama, H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228−8237. (b) Smith, A. B., III.; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255. See also references therein.

(6) (a) Rivkin, A.; Gonzalez-Lopez de Turiso, F.; Nagashima, T.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 3719−3725. (b) Rivkin, A.; Nagashima, T.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419−422.

(7) Harrison, C. A.; Jackson, P. M.; Moody, C. J.; Williams, J. M. J. *J. Chem Soc., Perkin Trans. 1* **1995**, 1131−1136.

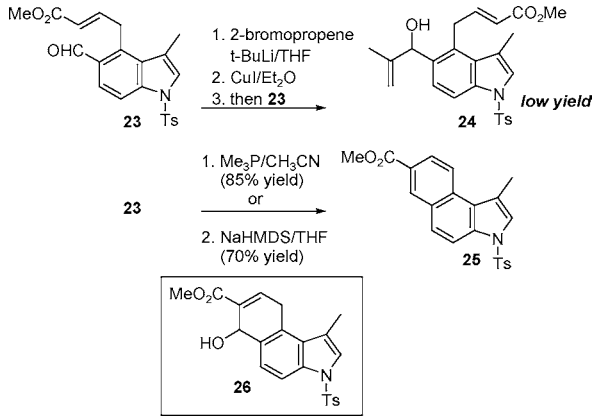
(8) The cleavage of dihydronaphthalenes (usually formed from a Birch reduction) to indoles is an old but rarely used indole synthesis called a Plieninger indolization. See: (a) Plieninger, H.; Voekl, A. *Chem. Ber.* **1976**, *109*, 2121−2125. (b) Plieninger, H.; Suhr, K.; Werst, G.; Kiefer, B. *Chem. Ber.* **1956**, *89*, 270−278.

(9) (a) England, D. B.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 6519−6522. (b) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215−1218. (c) Zawada, P. V.; Banfield, S. C.; Kerr, M. A. *Synlett* **2003**, 971−974. (d) Banfield, S. C.; England, D. B.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3325−3327.

a shorter route anyway because the aldehyde from formylation would have to be protected orthogonally from the acetaldehyde moiety at the indole 4 position. Methanolysis of the acetate in **20** and subsequent oxidation restored the necessary aldehyde, giving **21** in 75% yield. Horner–Emmons olefination of **21** smoothly produced enoate **22** in 87% yield. The requisite aldehyde at the indole 5 position was revealed by oxidative cleavage of the double bond in a two-step dihydroxylation/periodate cleavage protocol (71% overall). With **23** in hand, the stage was set for an isopropenyl cuprate addition and a subsequent aldol reaction.

Our initial experiments to install an isopropenyl moiety via cuprate addition were unsuccessful and resulted in a complex mixture, yielding **24** in small amounts (via nucleophilic addition to the aldehyde, Scheme 4). We then turned

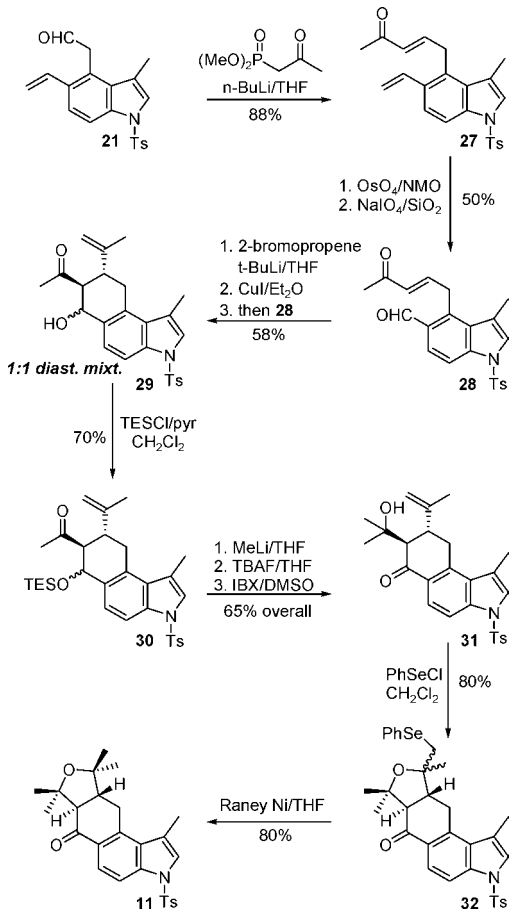
Scheme 4. Attempted Ring Closures



to a strategy which would see the benzofused ring in **11** formed prior to the installation of the isopropenyl group, ideally furnishing a compound such as **26** which would act as a Michael acceptor for an isopropenyl cuprate. To this end, **23** was treated with trimethylphosphine in acetonitrile to effect a Morita–Baylis–Hillman-type ring closure.[10] This proceeded in excellent yield; however, subsequent dehydration could not be avoided and the aromatized compound **25** was formed as the sole identifiable product. Other Morita–Baylis–Hillman conditions led to no appreciable reaction. Next, we turned to a strategy which would see cyclization via an extended enolate. Deprotonation of **23** with NaHMDS led to the relatively clean formation of the same product **25**.

At this stage, we reexamined the cuprate addition to a substrate such as **27**. It was felt that a better Michael acceptor may avoid the domination of 1,2-addition. To this end, aldehyde **21** was treated with a ketophosphonate to give enone **27** in 88% yield (Scheme 5). Selective dihydroxylation of the styrenyl moiety followed by oxidative cleavage gave a 50% yield of the aldehyde **28**. The modest yield of **28** arises from the formation of a side product where the

Scheme 5. Successful Synthesis of the Western Half of Lolicine A



benzylic hydroxyl group of the diol (en route to **28**) adds in a conjugate fashion to the enone. Careful control of the reaction conditions avoided this as a major difficulty.[11] Gratifyingly, cuprate addition to enone **28** not only installed the requisite isopropenyl moiety but also resulted in the addition of the intermediate enolate to the aldehyde in a tandem fashion.[12] The net result was the formation of **29** (58% overall as a 1:1 mixture, epimeric at the hydroxyl group) with a benzofused ring and suitable functionality for elaboration of the tetrahydrofuran ring. The 1:1 epimeric mixture of benzylic alcohols was inconsequential because that stereocenter would ultimately be a carbonyl group.

Protection of the benzylic hydroxyl group in **29** as a triethylsilyl ether yielded **30** in 70% yield which in turn was subjected to treatment with methyllithium, desilylation, and oxidation with IBX to give hydroxyl ketone **31** in 65% overall yield. All attempts to effect tetrahydrofuran formation with protic or Lewis acids led to dehydration via elimination of the hydroxyl group, sometimes with subsequent aroma-

(10) (a) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (b) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687–3690.

(11) The 50% yield obtained, although moderate, is an optimized and reproducible yield and is a preferable alternative to a more circuitous protection/deprotection route.

(12) This type of Michael-initiated ring-closure (MIRC) strategy for the formation of carbocycles has been known for some time. For a seminal contribution, see: Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, 2609–2612.

tization of the tetralone. The required ring closure, however, was effected with a selenoetherification protocol[13] to give selenide **32** in 80% yield which was reductively deselenated with Raney nickel to produce the target molecule **11** in 80% yield.

The fact that the trans stereochemistry in **11** was obtained was confirmed by comparison to the NMR data for the natural products. Both cis and trans relative stereochemistries at C31−C35 are found in nature, and the vicinal coupling constants between these two methines are, as expected, quite different. Figure 2 shows representations of lolicine A 11-*O*-propionate and lolitrem N 10-*O*-propionate as well as of our synthetic model **11**. The proton chemical shift at the C31 methine for lolicine A is 2.77 ppm and has a 14.1 Hz coupling to the C35 methine proton (2.68 ppm). The C31−C35 trans compound lolitrem N on the other hand has a proton chemical shift at C31 of 3.35 ppm and has a much smaller 7.3 Hz vicinal coupling to the C35 methine proton (2.68 ppm). Our compound **11** has a chemical shift for the C31 methine (lolicine numbering) of 2.72 ppm and has a 14.6 Hz vicinal coupling to the C35 methine proton (2.61−2.56 ppm). These values are very close to those for lolicine A 11-*O*-propionate, and therefore we are reasonably well assured that we have a trans relative stereochemistry at what would be the C31−C35 ring junction.

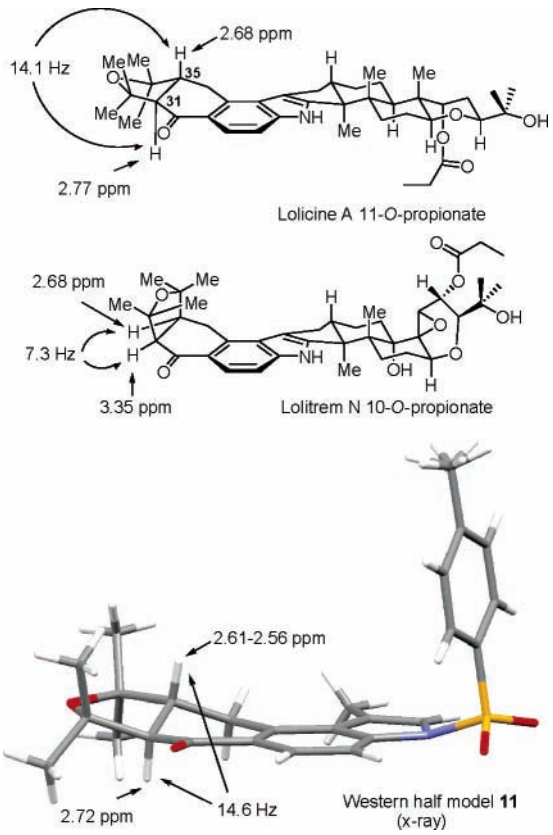


Figure 2. X-ray structure of **11** and comparison of NMR data to the natural products.

We were subsequently able to prepare crystals of **11** of a sufficient quality for X-ray analysis to confirm the relative trans stereochemistry of the C31−C35 ring fusion.[14] Far from being redundant, the X-ray analysis in concert with the NMR analysis acts as fairly conclusive evidence that lolicine A and related compounds have, in fact, the trans stereochemistry at C31−C35. To date, X-ray analysis of the natural products has not been possible.

In conclusion, we have developed an efficient synthesis of the western half of lolicine A and related compounds. A Diels−Alder/Plieninger indolization allows for the preparation of a suitably substituted indole which in turn sets the stage for the key tandem conjugate addition/aldol cyclization. This step sets the relative stereochemistry at the tetrahydrofuran in the trans relationship found in the natural product. We intend to use this synthetic sequence in our efforts to prepare lolicine A.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds are available as well as the X-ray cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060338J

(13) Nicolaou, K. C.; Lysenko, Z. *Tetrahedron Lett.* **1977**, 1257−1260.

(14) The representation of **11** shown in Figure 2 was generated from the cif file directly using Mercury (version 1.4.1) software. The methyl substituent on the *p*-toluene sulfonyl group shows disorder.