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# A Short Stereoselective Total Synthesis of the Fusarium Toxin Equisetin

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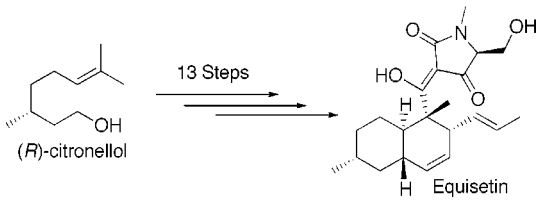
## ABSTRACT




**A short stereoselective synthesis of the fusarium toxin equisetin, an *N*-methylserine-derived acyl tetramic acid and potent inhibitor of HIV-1 integrase enzyme, is described using as the key step a stereoselective lithium perchlorate mediated intramolecular Diels−Alder reaction of a fully conjugated *E*,*E*,*E*-triene with a trisubstituted $\gamma$,$\delta$-unsaturated $\beta$-ketothioester.**

The fusarium toxin equisetin **1**, a fungal metabolite first isolated in 1974 from the white mold *Fusarium equiseti*,[1] exhibits an impressive range of biological properties,[2−4] including antibiotic and HIV inhibitory activity, cytotoxicity, and mammalian DNA binding. Equisetin falls into the acyl tetramic acid[5] class of natural products by virtue of its *N*-methylserine-derived heterocycle which in turn is fused to a quaternary stereogenic center of a trans octalin skeleton additionally substituted with two methyl and one propenyl groups. This exquisite three-dimensional structuring, combined with the diverse biological profile and the potential to exploit and develop methodology within our group, made this natural product an ideal synthetic target.[6] Here we describe a short and stereoselective synthesis of equisetin, **1**.

The synthetic plan relied on a late stage Lewis acid mediated intramolecular Diels−Alder (IMDA) reaction of **2** in which all carbons barring those of the *N*-methylserine component would be brought together to yield the appropriately decorated octalin skeleton,[7−8] suitably poised for transformation to the target compound. More specifically, it was believed that the fully conjugated all-*E* triene would undergo a stereoselective cycloaddition[9] with the attached trisubstituted $\gamma$,$\delta$-unsaturated $\beta$-ketothioester in which the configurations of the four newly formed stereogenic centers would be controlled by the methyl substituent adopting a pseudoequatorial position during the transition state. It was envisaged that this cycloaddition precursor would be readily synthesized through sequential manipulation of the hydroxyl

(1) Burmeister, H. R.; Bennet, G. A.; Vesonder, R. F.; Hesseltine, C. W. *J. Antimicrob. Agents Chemother*. **1974**, *5*, 634.
(2) Vesonder, R. F.; Tjarks, L. W.; Rohwedder, W. K.; Burmeister, H. R.; Laugal, J. A. *J. Antibiot. Agents Chemother*. **1979**, *32*, 759.
(3) Phillips, N. J.; Goodwin, J. T.; Fraiman, A.; Cole R. J.; Lynn, D. G. *J. Am. Chem. Soc.* **1989**, *111*, 8223.
(4) Singh, S. B.; Zink, D. L.; Goetz, M. A.; Dombrowski, A. W.; Polishook, J. D.; Hazuda, D. J. *Tetrahedron Lett.* **1998**, *39*, 2243.
(5) For references to representative members of this class of natural products, see: (a) Dixon, D. J.; Ley, S. V.; Gracza T.; Szolcsanyi, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 839. (b) Dixon, D. J.; Ley, S. V.; Longbottom D. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2231 and references therein.
(6) For proof of stereochemistry and the only total synthesis to date, see: Turos, E.; Audia J. E.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1989**, *111*, 8231.
(7) For related work, see: (a) Roush, W. R. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, New York, Seoul, Tokyo, 1991; Vol. 5, p 513 and references therein. (b) Witter D. J.; Vederas, J. C. *J. Org. Chem*. **1996**, *61*, 2613. (c) Shing, T. K. M.; Yang, J. *J. Org. Chem*. **1995**, *60*, 5785.
(8) For a recent review, see: Fallis, A. G. *Acc. Chem. Res*. **1999**, *32*, 464 and references therein.
(9) For work relating the lactone−enolate Claisen rearrangement of ref 6 to the cycloaddition approach adopted here for the preparation of trans-fused carbocyclic systems, see: Burke, S. D.; Piscopio A. D.; Kort, M. E.; Matulenko, M. A.; Parker M. H.; Armistead, D. M.; Shankaran, K, *J. Org. Chem*. **1994**, *59*, 332.

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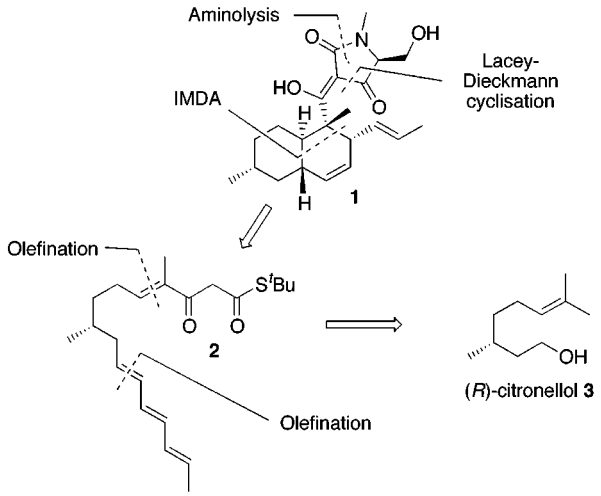
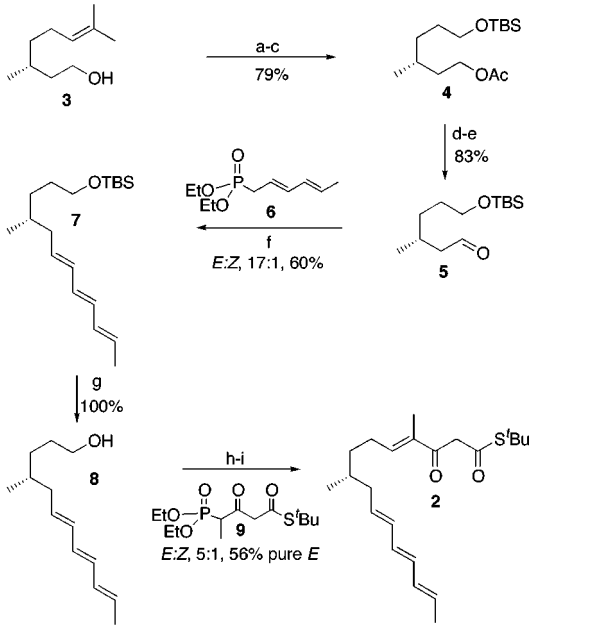
and alkene functionality[10] of commercially available (*R*)-citronellol, **3** (Scheme 1).

**Scheme 1**




**Scheme 2**[a]




[a] Reagents and conditions: (a) $Ac_2O$, Py, $CH_2Cl_2$; (b) $O_3$, $CH_2Cl_2$, −78 °C, then MeOH, $NaBH_4$, 0 °C; (c) TBSCl, Im, THF, rt; (d) MeOH, $K_2CO_3$, (cat.) rt; (e) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C to rt; (f) **6**, BuLi, THF, −78 °C to rt; (g) TBAF, THF, rt; (h) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C to rt; (i) **9**, BuLi, THF, HMPA, −78 °C to rt.

The synthetic route began with a simple acetylation of **3** using acetic anhydride and pyridine in dichloromethane at room temperature. This was followed by a standard reductive ozonolysis and subsequent hydroxyl protection with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide at room temperature to afford the differentially protected diol **4** in good yield over the three steps. This material was then quantitatively deacetylated under the Zemplin conditions, and the resulting alcohol was oxidized using the Swern protocol to give the desired aldehyde **5** in 83% yield (Scheme 2).

A number of olefination reactions on aldehyde **5** were attempted, with the ultimate goal being the production of the fully conjugated all-*E* triene required for the key intramolecular Diels−Alder step. However, the best conditions relied on the sequential treatment of a THF solution of isomerically pure diethyl (*E*,*E*)-2,4-hexadienyl phosphonate **6** with butyllithium at −78 °C, followed by addition of aldehyde **5** and warming the reaction mixture from −78 °C to room temperature. Using this method, a 17:1 mixture of inseparable *E*:*Z* isomers was produced in 60% yield. Considering that all other attempts by us at producing this particular double bond resulted in poor *E*:*Z* ratios, a reproducible selectivity of 17:1 was very gratifying.

Conversion of triene **7** to the Diels−Alder precursor **2** was achieved with minimal effort. First, standard TBS removal with TBAF in THF at 0 °C overnight gave the respective alcohol as a crystalline solid in quantitative yield. This was especially convenient as a single recrystallization from pentane removed the undesired *Z*,*E*,*E*-triene isomer produced in the previous step. Second, oxidation of alcohol **8** to the respective aldehyde using the Swern protocol proceeded without incident. Finally, a Horner−Wadsworth−Emmons reaction of this aldehyde and the dilithio anion of *tert*-butyl $\beta$-keto-$\gamma$-diethylphosphonothiolate **9**[11] produced a 5:1 mixture of isomers in favor of the *E* isomer. Surprisingly, these isomers were readily separated by silica gel chromatography and the desired Diels−Alder precursor **2** was isolated isomerically pure in 56% yield over two steps.

With substantial quantities of isomerically pure polyene in hand, the intramolecular Diels−Alder reaction was then studied. Whereas initial investigations using some aluminum-derived Lewis acids led to decomposition, it was found that dissolution of **2** in a 5 M ethereal solution of lithium perchlorate at room temperature for 17 h smoothly effected the cyclization process,[12] producing **10** in 70% yield and in >90% de. The notable levels of diastereocontrol in the intramolecular Diels−Alder reaction presumably arise from the stereogenic methyl group adopting a pseudoequatorial disposition in a well-organized chairlike transition state. Additionally, the lithium cation activated dieneophile must adopt an *endo* approach to the "diene" of the conjugated *E*,*E*,*E*-triene (Figure 1).

Conversion of this suitably decorated octalin skeleton to equisetin was possible by following three established trans-

(10) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, *2*, 117.

(11) Hayashi Y.; Narasaka, K. *Chem. Lett.* **1998**, 313. See also: Ley S. V.; Woodward P. R. *Tetrahedron Lett.* **1987**, *28*, 345.

(12) For recent examples of the use of lithium perchlorate (5 M in diethyl ether) in accelerating or promoting the intramolecular Diels−Alder reaction, see: (a) Saito, N.; Grieco, P. A. *J. Synth. Org. Chem.* **2000**, *58*, 39. (b) May, S. A.; Grieco, P. A.; Lee, H. H. *Synlett* **1997**, 493 (c) Grieco, P. A.; Nunes J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595 and references therein.

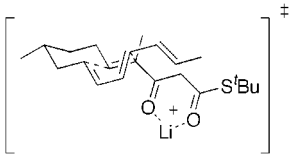


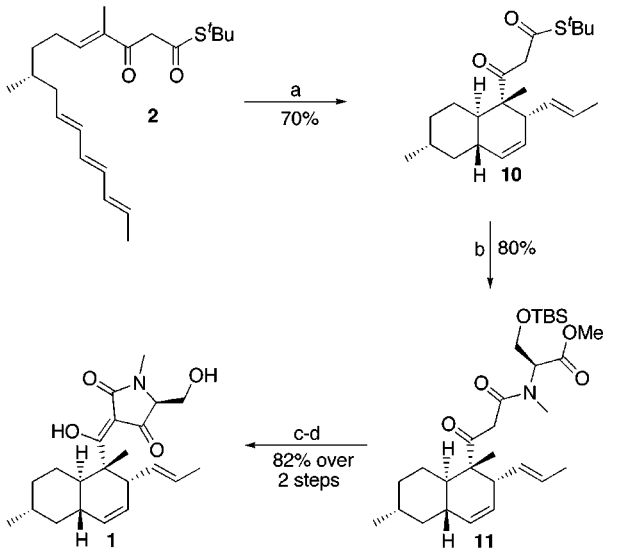

**Figure 1.**

formations. First, direct aminolysis of the *tert*-butyl thioester moiety with *O*-*tert*-butyldimethylsilyl *N*-methylserine methyl ester mediated by silver trifluoroacetate following the protocol introduced by our group[13] afforded $\beta$-keto amide **11** in excellent yield. Then, by following closely the two-step method of Danishefsky and co-workers[6] in the first synthesis of equisetin, a near quantitative removal of the *tert*-butyldimethyl silyl protecting group with hydrofluoric acid in acetonitrile at room temperature for 15 min gave the intermediate hydroxy compound. Treatment with excess sodium hydride in dichloromethane at 0 °C to room temperature over 30 min afforded, after purification by preparative TLC (silica gel eluting with 5% methanol in benzene), equisetin, **1**, as a colorless oil in 85% yield. The $^1$H NMR, IR, LRMS, and HRMS spectra and the specific rotation $[\alpha]^{28}_D$ −262 (*c* 0.038, $CHCl_3$) [lit.[6] $[\alpha]^{23}_D$ −253 (*c* 0.038, $CHCl_3$)] of synthetic equisetin were in excellent agreement with the data reported for the natural product (Scheme 3).

In summary, a short stereoselective synthesis of equisetin has been achieved using as the key step a lithium perchlorate mediated intramolecular Diels−Alder reaction of a fully conjugated *E*,*E*,*E*-triene with a trisubstituted $\gamma$,$\delta$-unsaturated $\beta$-ketothioester. This Diels−Alder precursor in turn was readily obtained through manipulation of (*R*)-citronellol, and

(13) Ley S. V.; Woodward P. R. *Tetrahedron Lett*. **1987**, *28*, 3019.

**Scheme 3**[a]




[a] Reagents and conditions: (a) $LiClO_4$, $Et_2O$, rt, 17 h; (b) (*S*)-*N*-methyl-*O*-*tert*-butyldimethylsilyl serine methyl ester, $CF_3CO_2Ag$, THF, $Et_3N$, 0 °C; (c) HF, $CH_3CN$, rt; (d) NaH, $CH_2Cl_2$.

the ideally decorated cycloaddition product was easily converted to the natural product in three subsequent steps.

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**Supporting Information Available:** Characterization data for equisetin, **1**, and synthetic intermediates **2**, **4**, **5**, **7**, **8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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