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Enantiospecific Formal Total Synthesis of (+)-Fawcettimine

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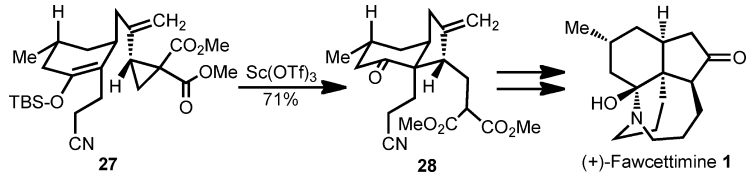
ABSTRACT



The diastereospecific attack of the silyl enol ether on the activated cyclopropyl diester 27 generated the hydrindanone 28 with complete stereocontrol. Thermal decarbomethoxylation of 28 gave the monoester 29, a key intermediate in Heathcock's synthesis, thereby completing a formal total synthesis of (+)-fawcettimine 1. The analogous cyclization of 33, the diastereomer of 27, afforded the diastereomeric diester 34, thereby demonstrating that the cyclization process is diastereospecific.

(+)-Fawcettimine **1** is a tetracyclic alkaloid belonging to the *Lycopodium* class of alkaloids and was isolated in 1959 by Burnell (Figure 1).[1] It exists predominantly as the carbinolamine, and the first total synthesis by Heathcock and coworkers proved the stereochemistry at C4.[2] Because of its challenging tetracyclic structure and postulated role as a biosynthetic precursor to additional members of the *Lycopodium* family, it has generated considerable synthetic interest.[3] We now report the enantiospecific formal total synthesis of (+)-fawcettimine **1** intercepting the Heathcock ester intermediate **29**.

Recently we reported[4] the acid-promoted stepwise Mukaiyama−Michael addition of hindered silyloxy dienes **5** to hindered enones **4** to give the formal cycloadduct **7** via the initial Mukaiyama−Michael adduct **6** (Scheme 1). For (+)-fawcettimine, a similar double addition process was conceived, this time with the cyclopropyl silyl enol ether **8**

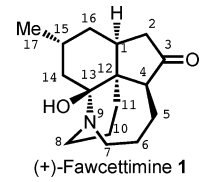


Figure 1

and enone **9** to access the hydrindanone core **11** by a tandem Mukaiyama−Michael homo-Michael process via the intermediate **10** (Scheme 2). Donor−acceptor (DA) cyclopropanes,[5] including cyclopropane-1,1-diesters, are known to undergo a wide array of reactions that include [3 + 2] and [4 + 3] cycloadditions leading to a variety of heterocycles, radical ring-openings, nucleophilic ring-openings, and metal-mediated coupling reactions;[6] however, an annulation of this

(1) Burnell, R. H. *J. Chem. Soc.* **1959**, 3091–3093.
(2) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548–1562.
(3) (a) Nishio, K.; Fujiwara, T.; Tomita, K.; Ishii, H.; Inubushi, Y.; Harayama, T. *Tetrahedron Lett.* **1969**, *10*, 861–864. (b) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671–7673. (c) Liu, K.-M.; Chau, C.-M.; Sha, C.-K. *Chem. Commun.* **2008**, 91–93.
(4) Jung, M. E.; Ho, D. *Org. Lett.* **2007**, *9*, 375–378.
(5) For reviews on donor−acceptor cyclopropanes, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (d) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (e) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72. (f) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060.

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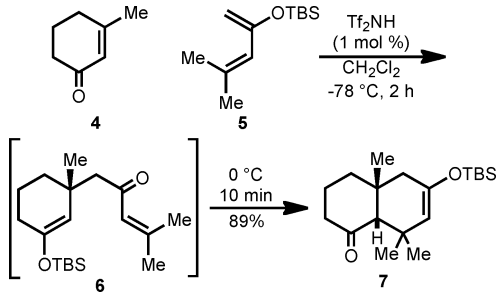
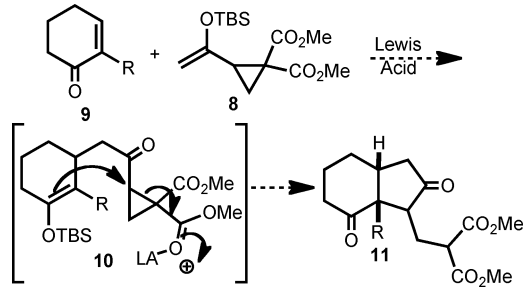
Scheme 1



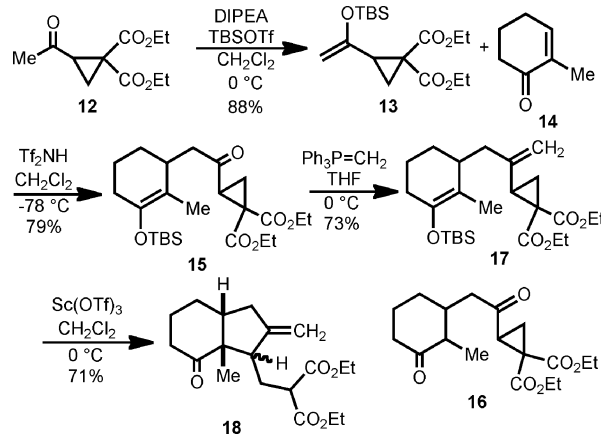
type has not been previously reported to our knowledge. Only two references have cited the attack of silyl enol ethers on cyclopropane-1,1-diesters, but in both cases the reactions were intermolecular.[7] Therefore, we decided to test the viability of this idea using a model system.

Scheme 2



Thus, the known methyl ketone **12**[8] was converted to the kinetic (and thermodynamic) TBS silyl enol ether **13** by treatment with TBSOTf and Hünig's base (Scheme 3). Triflimide-mediated Mukaiyama−Michael addition[4] of **13** to 2-methylcyclohexenone **14** gave the ketone **15** as a mixture of diastereomers. Warming the reaction mixture did not afford the cyclopropane ring-opened product but instead gave the silyl enol ether hydrolysis product **16**. Various fluoride reagents and Lewis acids were screened, but none of the conditions gave the annulated product and, in most cases, gave only the product of hydrolysis. To increase the reactivity

Scheme 3



of the system, the ketone **15** was subjected to standard Wittig methenylation conditions to give the 1,1-disubstituted olefin **17** in 73% yield. Treatment of **17** with a catalytic amount (20 mol %) of $Sc(OTf)_3$ gave the desired hydrindanone product **18** in 71% yield as a single regioisomer. To our knowledge, this is the first example of an intramolecular attack of a silyl enol ether on a cyclopropane-1,1-diester resulting in a new carbon−carbon bond to give an annulated product.

Encouraged by the results in the model system, we decided to demonstrate the utility of this method in a formal total synthesis of (+)-fawcettimine. Since only one regioisomer was obtained, we could safely rule out any "S_N2'-like" or "S_N1'-like" reaction mechanisms. Previous work[9] done in this area on intermolecular cyclopropane-1,1-diester ring openings allowed us to postulate that the key ring-opening reaction occurred via a stereospecific S_N2-like mechanism as shown in Figure 2. Thus, Lewis acid complexation of one (or both) of the two esters of **A** would be followed by attack of the silyl enol ether on the activated allylic cyclopropyl-1,1-diester **B** without any loss of stereocontrol to give stereospecifically **C**. To test this hypothesis, we decided to synthesize one diastereomer of the substrate and see if there were any loss of stereochemistry in the cyclized product.

After a simple molecular model analysis, it was determined that the previously unreported (*S*)-methyl ketone **23** was

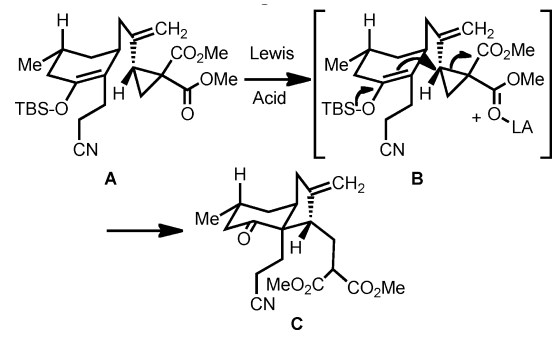


Figure 2

(6) For selected examples see: (a) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201. (b) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242–8244. (c) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023–3026. (d) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015. (e) Korotkov, V. S.; Larionov, O. V.; Hofmeister, A.; Magull, J.; de Meijere, A. *J. Org. Chem.* **2007**, *72*, 7504–7510. (f) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650. (g) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689–692. (h) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1107–1110. (i) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 4354–4357.

(7) (a) Fang, J.; Ren, J.; Wang, Z. *Tetrahedron Lett.* **2008**, *49*, 6659–6662. (b) Qu, J.-P.; Deng, C.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 7684–7689.

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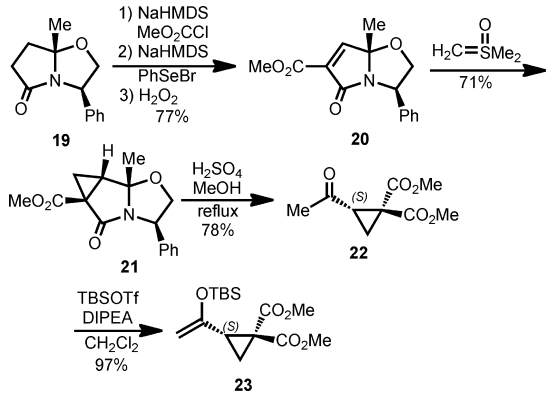
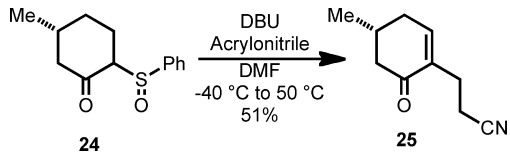
Scheme 4



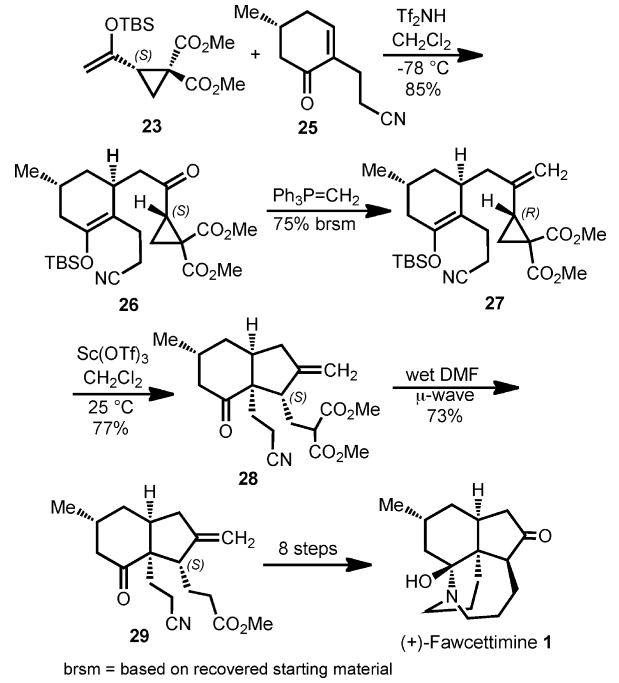
required to intercept Heathcock's intermediate **29** for the formal synthesis of fawcettimine **1**. Thus, the known bicyclic lactam **19** was treated sequentially with sodium hexamethyldisilazide, methyl chloroformate, and phenylselenenyl bromide, followed by an oxidative workup to give the α,β-unsaturated amide **20** in 77% yield (Scheme 4). Subjecting this very activated alkene **20** to standard Corey−Chaykovsky conditions gave the cyclopropane **21** as a single diastereomer. Hydrolysis of **21** in acidic methanol gave the methyl ketone **22** which was identical in all respects to the known (*R*) enantiomer, except for optical rotation.[10] Finally, treatment of **22** with TBSOTf and Hünig's base gave the desired kinetic TBS silyl enol ether **23**.

Scheme 5



The enone **25** required for the (+)-fawcettimine synthesis was obtained by Michael addition of the known sulfoxide **24** to acrylonitrile followed by thermal sulfoxide elimination in 51% yield[11] (Scheme 5). The enone **25** and the silyl enol ether **23** were then treated with triflimide to give the corresponding ketone **26** as a single diastereomer (Scheme 6). Wittig methenylation of **26**, though sluggish, afforded the desired olefin **27** in 75% yield (based on recovered starting material). To our delight, treatment of **27** with $Sc(OTf)_3$ afforded cleanly the cyclopropane ring-opened product **28** in 77% yield as a single diastereomer. Thus this annulation had proceeded with complete stereocontrol in this system. To finish the formal total synthesis of **1**, subjection of **28** to modified Krapcho decarboxylation conditions[12] gave, in 73% yield, the ester **29**, which was identical in all respects to the ester previously reported by Heathcock,[2] indicating that our molecular modeling prediction was correct.

Scheme 6



Even though the Lewis acid-promoted intramolecular ring-opening cyclization of **27** to give **28** had proceeded with complete stereocontrol, we could not guarantee that this result was not due to a "matched" diastereoselective process or to kinetic control rather than a truly diastereospecific process. Therefore, to prove that the observed stereospecificity of the cyclization was not attributed to the intrinsic diastereoselectivity of the substrate, we decided to prepare the epimeric cyclopropane **31** to synthesize the C4 epimer (fawcettimine numbering) **34**. Thus, the known (*R*) methyl ketone **30**[13] was synthesized according to the procedure of Meyers and then treated with TBSOTf and Hünig's base to give the corresponding kinetic (*R*) silyl enol ether **31** (Scheme 7). Triflimide-mediated Mukaiyama−Michael addition of the silyl enol ether **31** to the enone **25** afforded the ketone **32**. Wittig methenylation gave in 70% yield (brsm) the olefin **33**, which on treatment with $Sc(OTf)_3$ afforded **34** as a single diastereomer. Comparison of the spectroscopic data clearly indicated that **34** was not identical to the previously prepared malonate **28** and thus the ring opening was completely diastereospecific. Although we have not carried this compound forward, it is possible that compound **34** could still be a viable intermediate toward the synthesis of (+)-fawcettimine **1** based on the previous Heathcock synthesis.[2]

In summary, we have shown that the process of a stepwise Mukaiyama−Michael addition of the silyl enol ether of an

(9) (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650. (b) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597–8599.

(10) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814–3819.

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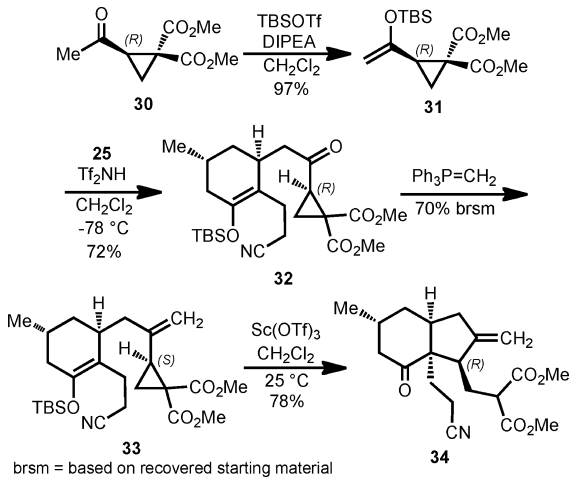
Scheme 7



acetylcyclopropane-1,1-dicarboxylate, Wittig olefination, and final Lewis-acid-promoted cyclopropane opening affords hydrindanones in good yield and with complete diastereocontrol. Furthermore, we have shown that this process proceeds via an "S_N2-like" mechanism (Figure 2) and is therefore completely diastereospecific with full retention of the stereochemistry of the cyclopropyl center. Lastly, we have completed a formal total synthesis of (+)-fawcettimine **1**.

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Supporting Information Available: Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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