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Synthetic Studies toward FR182877. Remarkable Solvent Effect in the Vinylogous Morita–Baylis–Hillman Cyclization

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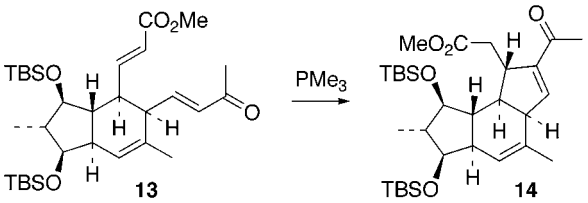
ABSTRACT



The intramolecular vinylogous Morita–Baylis–Hillman reaction was explored to access the central cyclopentane ring of FR182877. The reaction manifold and product distribution is strikingly solvent and substrate dependent.

The importance of antimitotic drugs in cancer chemotherapy prompted screening of a strain of *Streptomyces* by scientists at Fujisawa Pharmaceutical Co., resulting in the isolation of a new antimitotic agent FR182877.[1] FR182877 exhibits potent antitumor activities against a broad range of cancer cells, promoting microtubule assembly in vitro and inducing G_2/M phase arrest in the cell cycle.

FR182877 possesses an unprecedented hexacyclic structure containing a strained tetrasubstituted olefin, which readily oxidizes in the presence of oxygen to give a stable bioinactive epoxide.[1c] Combining both high biological activity and an unusual architecture, FR182877 has attracted considerable synthetic interest.[2] Thus far, two total syntheses of FR182877 have been achieved, both of which feature an elegant tandem transannular Diels−Alder/hetero-Diels−Alder reaction sequence.[3]

Our strategy calls for the *as*-indacene ring system of FR182877 to be generated by the intramolecular vinylogous Morita−Baylis−Hillman cyclization[4] of **1** (Figure 1). Intermediate **1**, in turn, would be assembled by an intramolecular Diels−Alder/macrolactonization sequence. We report herein

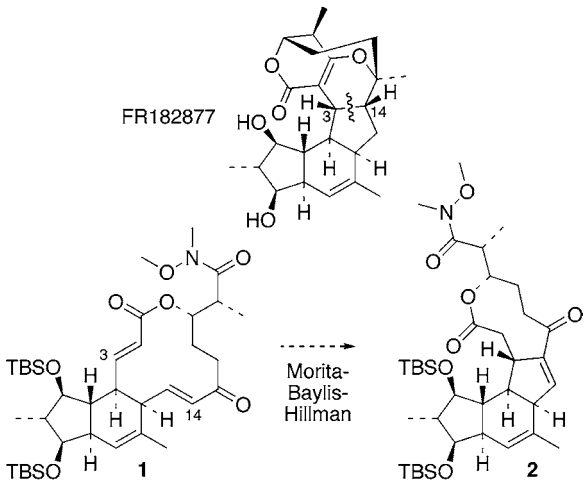


Figure 1. Key disconnection of FR182877.

(1) (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto; S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123. (b) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204. (c) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615. (d) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2002**, *55*, C-1.

(2) (a) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999**, *1*, 645. (b) Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585. (c) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307. (d) Clarke, P. A.; Davie, R. L.; Peace, S. *Tetrahedron Lett.* **2002**, *43*, 2753. (e) Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2002**, *43*, 3263.

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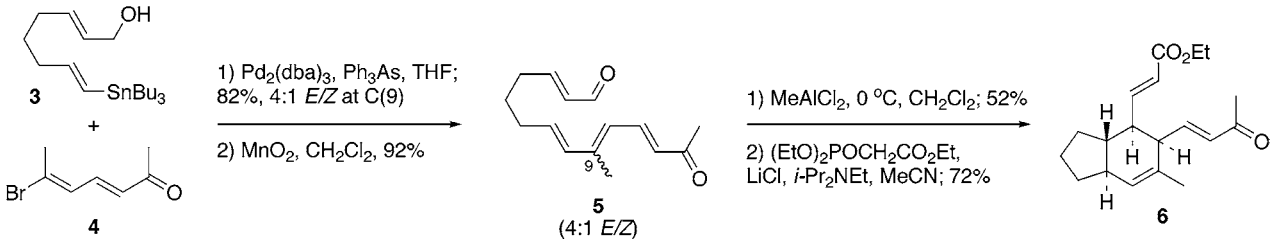
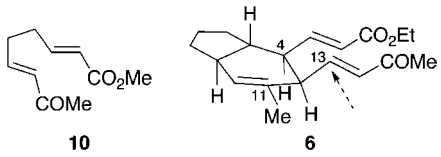
Scheme 1. Synthesis of **6**



our studies of the key Morita−Baylis−Hillman event, which shows that success of this reaction is highly solvent and substrate dependent.

We began by studying model enone-enoate **6**, which was prepared by an intramolecular Diels−Alder reaction[5] and Horner−Wadsworth−Emmons olefination[6] of aldehyde **5** (Scheme 1). Aldehyde **5**, in turn, was prepared as an inseparable 4:1 *E/Z* mixture at C(9) via Stille coupling[7] of vinylstannane **3** and bromodienone **4**, followed by oxidation of the allylic alcohol by MnO_2.[8]

Vinylogous Morita−Baylis−Hillman cyclization studies with **6** are outlined in Table 1. Conditions optimized[4b] for cyclization of **10**, specifically that involving trimethylphosphine catalysis in *tert*-amyl alcohol, resulted in a slow cyclization of **6** (entry 1).



A large excess of trimethylphosphine was required to consume the starting material. Nucleophilic attack of the phosphine onto C(13) of enone **6** is likely slowed by nonbonded interactions of PMe_3 with the nearby C(11) methyl group in the transition state. Examination of models suggests that the enone must rotate about the C(12)−C(13) bond to allow for phosphine addition at C(13) from the top or bottom faces. Either rotation, however, increases the ground-state nonbonded interaction between the C(13)−C(14) enone and the C(11) methyl group and/or the C(3)-enoate. These problems conspire to slow the rate of PMe_3 addition to C(13) of **6** such that competitive addition of the catalyst to C(3) initiates the cyclization to the undesired regioisomer **9**. Indeed, mixtures of the desired tricyclic enone **7** and undesired regioisomer **9** were obtained under many of the conditions examined. As expected on the basis of allylic strain considerations,[4c] single diastereomers of **7** and **9** were produced.

It is well-established that the choice of solvent has dramatic effects on the Baylis−Hillman reaction, since highly polarized intermediates are involved.[3d,9] Thus, a survey of various solvents was undertaken to increase the selectivity and efficiency for formation of the desired tricycle **7**. When methanol was used as a solvent, we observed transesterification, with olefin migration product **8** formed as a single diastereomer (entries 3 and 4). While reactions in ethanol behaved similarly, use of 2-propanol as a solvent gave a 1:1 mixture of **7** to **8** (entries 5 and 6). We were pleased that the cyclization in 2,2,2-trifluoroethanol was considerablely faster, due presumably to the hydrogen-bonding ability of this solvent, but were surprised that regioisomer **9** was formed as the sole product in this case (entry 7).

Reactions in the polar aprotic solvents NMP and HMPA gave olefin migration product **8** as the major product with better conversion occurring in the latter solvent (entry 9). Oddly, **9** was the major product in MeCN and a mixture was obtained in DMSO (entries 10 and 11).

Since olefin migration leading to **8** was prevented in *tert*-amyl alcohol, and formation of undesired regioisomer **9** was minimal in HMPA, we considered combinations of these solvents (entries 12 and 13); however, mixtures of **8** and **9** were obtained. No reaction was observed in CH_2Cl_2 or THF either at room temperature or at reflux. Mild Brønsted and Lewis acid acceleration has been reported for intermolecular Morita−Baylis−Hillman reactions using phenol in THF[10] and Et_3Al in CH_2Cl_2;[11] however, **6** did not react under these conditions.

Given the established rate acceleration of the Baylis−Hillman reaction by water,[12] it was gratifying that in 3:1

(3) (a) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552. (b) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787. (c) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.

(4) (a) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (b) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404. (c) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157. (d) For a recent review of the Baylis−Hillman reaction, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(5) Roush, W. R. Intramolecular Diels−Alder Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 513.

(6) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(7) For a related Stille coupling, see: Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417.

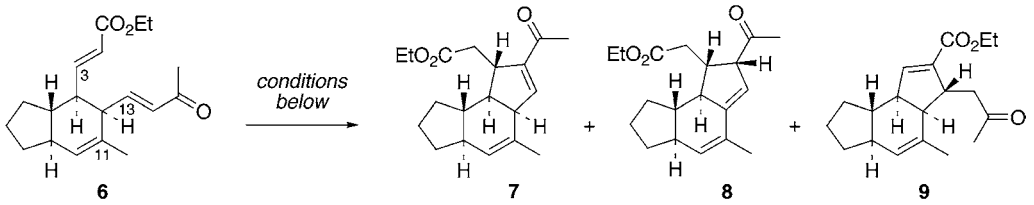
(8) Gritter, R. J.; Wallace, T. J. *J. Org. Chem.* **1959**, *24*, 1051.

(9) For recent studies, see: (a) Grainger, R. S.; Leadbeater, N. E.; Pamies, A. M. *Catal. Commun.* **2002**, *3*, 449. (b) Shi, M.; Xu, Y.-M.; Zhao, G.-L.; Wu, X.-F. *Eur. J. Org. Chem.* **2002**, 3666. (c) Hayashi, Y.; Okado, K.; Ashimine, I.; Shoji, M. *Tetrahedron Lett.* **2002**, *43*, 8683.

(10) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165.

(11) Imagawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, M. *Synth. Commun.* **1984**, *14*, 1267.

Table 1. Intramolecular Vinylogous Morita−Baylis−Hillman Reactions of **6**



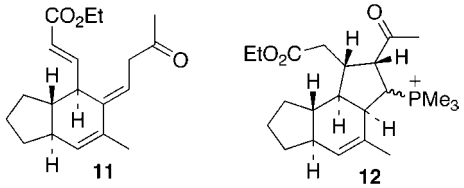
entry	catalyst (equiv)	solvent[a] (concn)	time (h)	recovered **6** (%)	yield of **7** + **8** + **9** (%)	ratio of **7**:**8**:**9**
1	PMe_3 (10)	*t*-amyl-OH (0.04 M)	18	11	71	58:8:34
2	PMe_3 (2)	*t*-amyl-OH (0.15 M)	18	10	64	50:6:44
3	PMe_3 (10)	MeOH (0.03 M)	1	0	63[b]	0:67:33
4	PMe_3 (1)	MeOH (0.03 M)	1	30[c]	nd	0:75:25
5	PMe_3 (10)	EtOH (0.03 M)	1	6	74	0:67:33
6	PMe_3 (2)	*i*-PrOH (0.03 M)	18	0	60	50:50:0
7	PMe_3 (10)	CF_3CH_2OH (0.03 M)	1	0	78	**0:0:100**
8	PMe_3 (10)	NMP (0.03 M)	18	46	24	0:90:10
9	PMe_3 (10)	HMPA (0.05 M)	18	0	65	**0:90:10**
10	PMe_3 (10)	MeCN (0.03 M)	18	9	74	0:25:75
11	PMe_3 (10)	DMSO (0.03 M)	18	13	49	38:38:24
12	PMe_3 (10)	1:1 HMPA/*t*-amyl-OH (0.03 M)	18	nd	nd	0:50:50
13	PMe_3 (10)	10:1 HMPA/*t*-amyl-OH (0.03 M)	18	nd	nd	0:75:25
14	PMe_3 (2)	3:1 THF/H_2O (0.04 M)	8	0	74	**100:0:0**
15	PMe_3 (1)	3:1 THF/H_2O (0.1 M)	8	7	68	**100:0:0**
16	PMe_3 (10)	3:1 THF/*t*-amyl-OH (0.03 M)	18	nd	nd	45:10:45
17	NEt_3 (20)	HMPA (0.03 M)	16	23	47	0:100:0
18	PhSLi (1)	THF (0.02 M)	12	0	55	0:100:0

[a] Thoroughly degassed by the freeze−pump−thaw method. [b] Isolated as methyl esters. [c] Isolated as a 3:1 mixture of ethyl/methyl esters.

THF−water, the rate of cyclization of **6** was dramatically increased. Most rewarding was that desired product **7** was obtained exclusively (entries 14 and 15). Furthermore, we were able to lower the phosphine loading to 1 equiv.[13] Replacing the THF/water mixture by THF/*tert*-amyl alcohol (entry 16) gave the same product distribution as observed in *tert*-amyl alcohol alone.

The stereoselective formation of olefin migration product **8** is intriguing. A reasonable first guess is that phosphine-mediated olefin migration of the Baylis−Hillman product **7** occurs as soon as it is formed, yet treatment of **7** with 20 equiv of trimethylphosphine in HMPA gave only a 30% conversion to **8** after 2 days.

A more likely possibility would be an olefin migration of the precusor enone **6** to undetected intermediate **11**,[14] a rapid Michael cyclization would then lead to **8**. This path is supported by the use of more basic reagents such as NEt_3 and PhSLi (entries 17 and 18). A third possibility for the generation of **5** involves a Hofmann elimination of the intermediate phosphonium salt **12**.[15] In protic solvents, the enolate derived from phosphine attack may be used to generate alkoxide, which in turn may behave as a general base.[16]



We next turned our attention to studies of a model system with the substitution pattern present in FR182877 (Scheme 2). We were pleased that the Morita−Baylis−Hillman reaction of **13**[17] in *tert*-amyl alcohol, 3:1 THF/water, and 2,2,2-trifluoroethanol all gave the desired product **14** with between 4:1 and 6:1 diastereoselectivity.[18] Again, allylic strain between the C(2)−C(3) olefin and the bicycle governed the stereochemical course of the cyclization. Neither the olefin migration product nor the product of ester cyclization

(12) (a) Byun, H.-S.; Reddy, K. C.; Bittman, R. *Tetrahedron Lett.* **1994**, *35*, 1371. (b) Auge, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* **1994**, *35*, 7947. (c) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413. (d) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369. (e) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687. (f) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723. (g) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510.

(13) A puzzling shift in reaction diastereoselectivity was observed by Yang and Chen in an intermolecular Baylis−Hillman catalyzed by DABCO in THF/water versus DMSO: Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729.

(14) Molecular modeling using Spartan (Monte Carlo search with MMF94) estimates a 5 kcal/mol preference for the (*E*)-olefin geometry as shown with **11**.

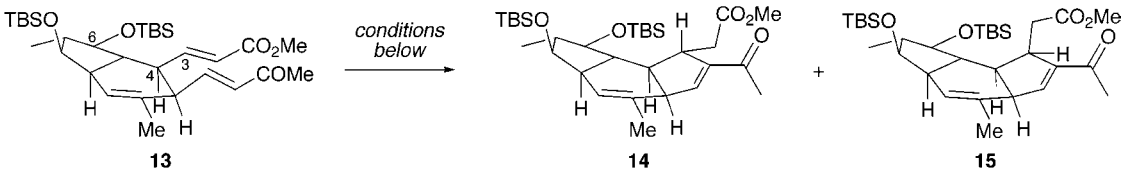
(15) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.

(16) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

(17) Our synthesis of **13** will be reported elsewhere.

(18) Tricycles **7**, **14**, and **15** are readily oxidized in the presence of air; see Supporting Information.

Scheme 2. Vinylogous Morita−Baylis−Hillman Reactions with a More Advanced System



10 equiv PMe_3, 0.03 M *t*-amyl-OH, 20 h: 56% (**14**:**15** = 6:1) plus 20% **13**
4 equiv PMe_3, 0.03 M 3:1 THF/H_2O, 12 h: 84% (**14**:**15** = 6:1)
10 equiv PMe_3, 0.03 M CF_3CH_2OH, 12 h: 62% (**14**:**15** = 4:1)

onto the ketone were observed; the latter was likely inhibited by the equatorially disposed silyloxy substituent at C(6) that slows the rate of PMe_3 addition to C(3) of **13**.

The *as*-indacene substructure of FR182877 has served as an instructive target for further development of the intramolecular vinylogous Morita−Baylis−Hillman reaction.[4b,c] The remarkable solvent effect on the reaction manifold discovered with **6** expands our insight into the factors that control this cyclization. The successful intramolecular cyclization of enone-enoate **13** is promising for our planned synthesis of FR182877.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for **3**−**9**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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