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Application of the Intramolecular Vinylogous Morita–Baylis–Hillman Reaction toward the Synthesis of the Spinosyn A Tricyclic Nucleus

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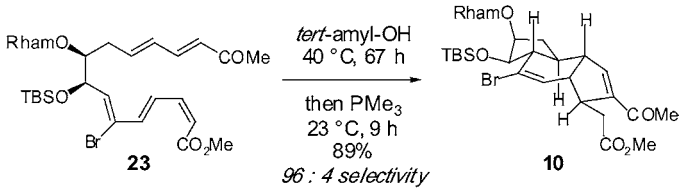
ABSTRACT



A concise synthesis of the spinosyn A tricyclic nucleus 27 has been developed by a route featuring a one-pot tandem intramolecular Diels–Alder reaction and intramolecular vinylogous Morita–Baylis–Hillman cyclization in which five stereocenters in tricycle 10 are set with excellent selectivity.

The spinosyns are a family of polyketide natural products possessing extraordinary insecticidal activity. The biosynthetic mixture, generated by *Saccharopolyspora spinosa*, is composed mostly of spinosyn A (**1**, Scheme 1) (ca. 85%) and spinosyn D (ca. 10−15%).[1] This mixture is currently marketed as the insecticide Spinosad for use against a variety of insects.[2] Total syntheses of spinosyn A have been reported by Evans and Paquette.[3]

We have recently reported a synthesis of the *as*-indacene ring system of spinosyn A in which the tricyclic framework **3** is assembled from macrolactone **2** via a transannular Diels−Alder reaction followed by a Claisen ring contraction (Scheme 1).[4] This strategy provided tricycle **3** with excellent stereocontrol. While in principle the macrocycle can be appended to **3** en route to completion of a total synthesis, we felt that a more succinct approach would be to incorporate the macrocycle prior to formation of the tricyclic core unit. Kirst has suggested that the biogenesis of spinosyn A may involve a transannular Diels−Alder reaction and a Michael ring closure of an appropriately functionalized macrocyclic pentaene.[5] Accordingly, our current synthetic strategy targets pentaene **5** as a substrate for the assembly of spinosyn via a tandem transannular Diels−Alder reaction and intramolecular vinylogous Morita−Baylis−Hillman cyclization sequence (Scheme 2). We report herein the successful application of this strategy in an intramolecular Diels−Alder manifold to the synthesis of the spinosyn A tricyclic nucleus.

We initially elected to explore the viability of the Diels−Alder sequence on the model tetraene **6**, which contains a

(1) (a) Kirst, H. A.; Michel, K. H.; Martin, J. W.; Creemer, L. C.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Jones, N. D.; Thompson, G. D. *Tetrahedron Lett.* **1991**, *32*, 4839. (b) Kirst, H. A.; Michel, K. H.; Mynderase, J. S.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Thompson, G. D. In *Fermentation-Derived Tetracyclic Macrolides*; 1992; pp 214−225. (c) Martynow, J. G.; Kirst, H. A. *J. Org. Chem.* **1994**, *59*, 1548. (d) Sparks, T. C.; Crouse, G. D.; Durst, G. *Pest Management Sci.* **2001**, *57*, 896. (e) Crouse, G. D.; Sparks, T. C.; Schoonover, J.; Gifford, J.; Dripps, J.; Bruce, T.; Larson, L. L.; Garlich, J.; Hatton, C.; Hill, R. L.; Worden, T. V.; Martynow, J. G. *Pest Management Sci.* **2001**, *57*, 177.

(2) Dagani, R. *Chem. Eng. News* **1999**, *77*, July 5, p 30.

(3) (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. (b) Paquette, L. A.; Gao, Z. L.; Ni, Z. J.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543. (c) Paquette, L. A.; Collado, I.; Purdie, M. *J. Am. Chem. Soc.* **1998**, *120*, 2553.

(4) Frank, S. A.; Roush, W. R. *J. Org. Chem.* **2002**, *67*, 4316.

(5) Kirst, H. A.; Michel, K. H.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Thompson, G. D. In *Microbial Metabolites*; Nash, C., Ed.; Wm. C. Brown: Dubuque, 1991; Vol. 32, p 109.

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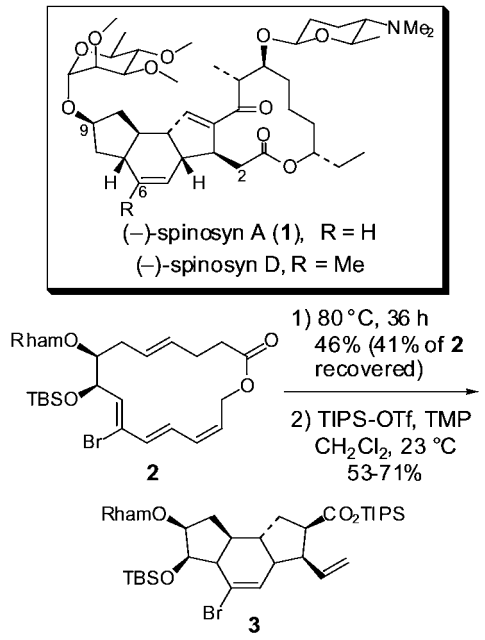
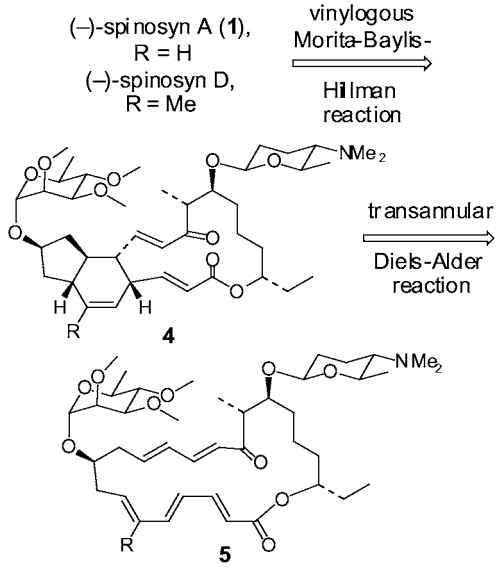
Scheme 1

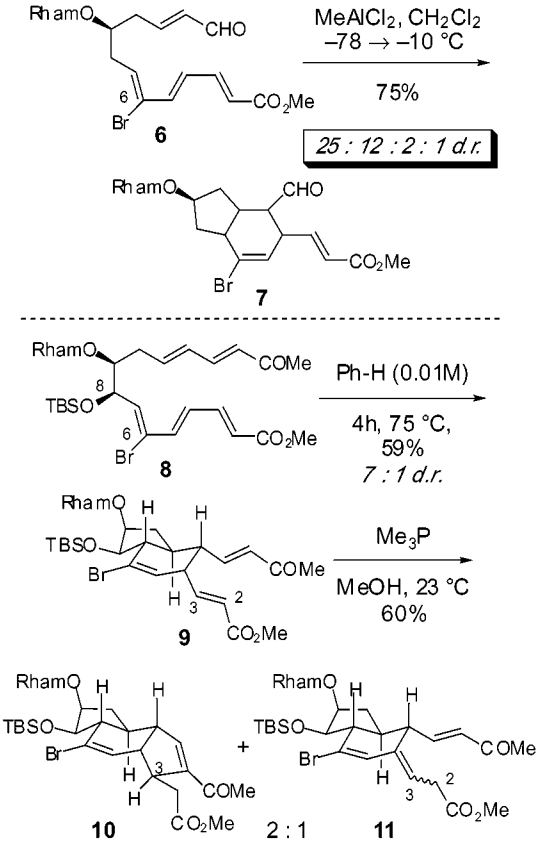


C(6)−Br steric directing group[6] for stereochemical control of the intramolecular Diels−Alder (IMDA) reaction. Unfortunately, this reaction proceeds with poor control of the C(7)−C(11) ring fusion stereochemistry relative to the preexisting C(9)-rhamnosyloxy substituent. While appending a bromine atom at C(6) afforded little stereocontrol by itself, installation of an additional C(8)-silyloxy substituent in pentaene **8** effectively regulated the stereochemistry of the IMDA reaction, which provided cycloadduct **9** as the major product of a 7:1 mixture of diastereomers from the thermal reaction (Scheme 3). The C(8)-silyloxy unit functions as a stereochemical control element in this case by introduction

Scheme 2. Biomimetic Strategy for Synthesis of (−)-Spinosyn A



Scheme 3



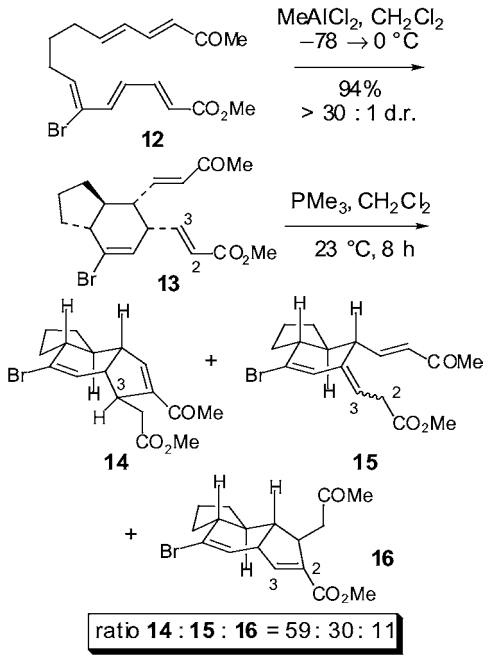
of 1,3-allylic strain interactions with the C(6)−Br group in the transition state leading to the minor product.[4,9]

However, attempts to apply the recently developed[7,8] intramolecular vinylogous Morita−Baylis−Hillman reaction to the Michael cyclization of **9** to **10** proved to be highly problematic. Surprisingly, treatment of **9** with Bu_3P in CH_3CN provided none of the desired tricycle **10** but rather **11** exclusively (80% yield) resulting from migration of the C(2)−C(3) olefin. However, use of Me_3P in MeOH provided a 2:1 mixture of tricycle **10** and the olefin migration product **11** in 60% yield.

A more readily accessible model system **13** (Scheme 4), lacking the C(9)-rhamnosyloxy substituent of **6**, was next prepared in an attempt to define conditions to minimize the problematic olefin migration reaction (cf., **9** → **11**). In the process of generating **13** we demonstrated that the Diels−Alder reaction of pentaene **12** can be performed under Lewis acid catalysis ($MeAlCl_2$, CH_2Cl_2, −78 °C), thereby providing cycloadduct **13** in 94% yield with >30:1 selectivity. Unfortunately, Me_3P-promoted cyclization of **13** in various solvents

(6) (a) Boeckman, R. K.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421. (b) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327. (c) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.
(7) Wang, L. C.; Luis, A. L.; Agaplou, K.; Jang, H. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402.
(8) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.
(9) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

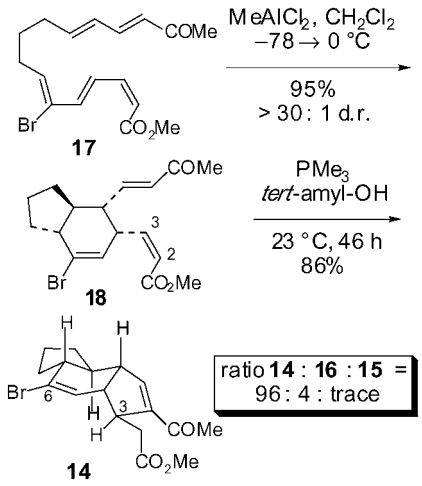
Scheme 4



gave mixtures of **14**−**16**. The best result was obtained when **13** was treated with Me_3P (1 equiv) in CH_2Cl_2, from which a ca. 2:1 mixture of the desired tricycle **14** and the olefin migration product **15** was obtained. Also produced was the regioisomeric tricycle **16**, which derives from initial addition of the phosphine catalyst to the enoate unit of **13**.[8]

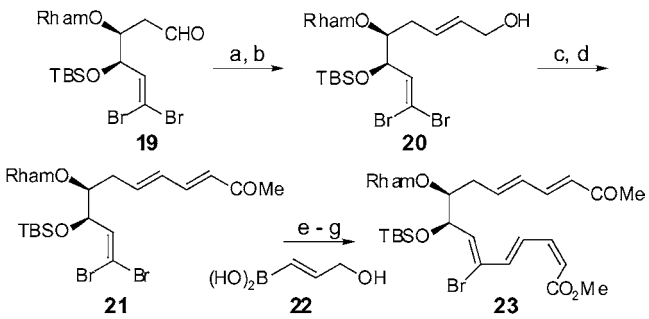
Conformational analysis of **13** suggested that changing the C(2)−C(3) olefin geometry from (*E*) to (*Z*) would change the orientation of C(4)-H relative to the C(2,3)-π-system owing to the need to minimize allylic strain interactions,[9] thereby disfavoring deprotonation of C(4)-H and suppressing the problematic olefin migration that occurs in the cyclizations of **9** to **10** (Scheme 3) and of **13** to **14** (Scheme 4). Accordingly perhydroindene **18** was synthesized to test this hypothesis (Scheme 5). Lewis acid promoted IMDA cyclization of **17** afforded **18** containing the targeted C(2,3)-(*Z*)-enoate unit in 95% yield and with >30:1 selectivity. When **18** was treated with 0.5 equiv of Me_3P in *tert*-amyl alcohol, olefin migration was negligible and tricycle **14** was obtained in 86% yield with 96:4 chemoselectivity (e.g., ratio **14**:**16**).

Scheme 5



With a solution to the olefin migration problem in hand, we set out to apply the tandem intramolecular Diels−Alder reaction and Morita−Baylis−Hillman cyclization strategy to the synthesis of the spinosyn tricyclic nucleus (Scheme 6).

Scheme 6[a]



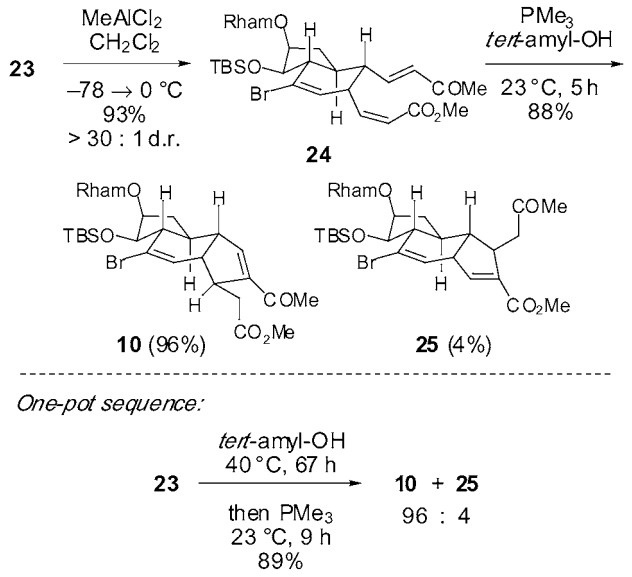
[a] (a) LiCl, DBU, $(MeO)_2P(O)CH_2CO_2Me$, CH_3CN, −40 → −20 °C, 14 h (86%); (b) DIBAL, CH_2Cl_2, −78 → 0 °C, 30 min (100%); (c) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 → 23 °C; (d) Ph_3P=CHCOMe, benzene, reflux, 85 h, (77% from **20**); (e) **22**, $(Ph_3P)_4Pd$, TlOEt, 3:1 THF/H_2O, 23 °C (63%); (f) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 → 23 °C; (g) $(CF_3CH_2O)_2P(O)$-CH_2CO_2Me, KHMDS, 18-Cr-6, THF, −78 °C, (57% over 2 steps).

Pentaene **23**, targeted as the substrate for the key cyclization sequence, was synthesized as summarized in Scheme 6. Horner−Wadsworth−Emmons olefination[10] of the known aldehyde **19** [4] gave the unsaturated ester in 86% yield, which was reduced to the allylic alcohol **20** in quantitative yield. Dess−Martin oxidation[11] of **20** followed by olefination using Ph_3P=CHCOMe afforded enone **21** in 77% yield. Suzuki coupling of **21** with vinyl boronic acid **22**[12] in the presence of TlOEt[13] provided the allylic alcohol in 63% yield. Oxidation of this intermediate to the aldehyde and subsequent (*Z*)-selective olefination using Still's protocol[14] provided pentaene **23** in 57% yield.

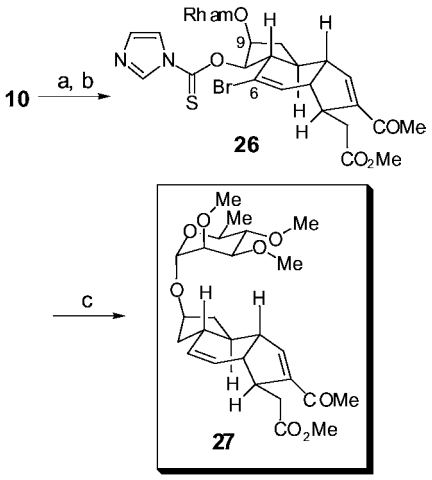
Treatment of **23** with $MeAlCl_2$ in CH_2Cl_2 at −78 °C generated the Diels−Alder product **24** in 93% yield with a diastereomeric ratio >30:1 (Scheme 7). The key intramolecular vinylogous Morita−Baylis−Hillman reaction was then performed by treating a solution of **24** in *tert*-amyl alcohol with Me_3P (0.5 equiv). This provided the desired tricyclic adduct **10** in 88% yield as a 96:4 mixture of

(10) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(12) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989.
(13) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.
(14) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

Scheme 7



Scheme 8[a]



[a] (a) HF·pyr, THF, 96%; (b) 1,1′ -thiocarbonyldiimidazole, DMAP, Ph-CH_3, 65 °C, 95%; (c) $(TMS)_3SiH$, AIBN, dioxane, 80 °C, 73%.

regioisomers. Only one diastereomer of **10** was observed by ^{1}H NMR analysis, indicating that the cyclization had generated the final stereocenter in the tricycle with at least 97:3 diastereoselectivity. We were intrigued by the possibility that the IMDA/Morita−Baylis−Hillman cyclization sequence might be effected in one pot. Indeed, when **23** was heated at 40 °C in *tert*-amyl alcohol for 67 h, after which Me_3P (0.6 equiv) was added at room temperature, tricycle **10** was obtained in 89% yield as a 96:4 mixture of regioisomers. The selectivity of the thermal intramolecular Diels−Alder reaction at 40 °C is ≥20:1.

With the *as*-indacene core assembled, removal of the two stereodirecting groups was performed (Scheme 8). Exposure of **10** to HF·pyridine liberated the C(8) alcohol in 96% yield. Subsequent treatment of this alcohol with 1,1′-thiocarbonyldiimidazole afforded **26** in 95% yield.[15] Finally, a one-pot deoxygenation and debromination reaction was effected by treatment of **26** with tris(trimethylsilyl)silane[16a,b] and AIBN in dioxane, which provided the spinosyn A tricyclic nucleus **27** in 73% yield.

(15) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

In conclusion, we have developed an intramolecular Diels−Alder reaction and Morita−Baylis−Hillman cyclization sequence for the synthesis of the spinosyn A tricycle **27**. The key tricyclic precursor **10** was assembled from **23** via a two-step sequence or a one-pot tandem cyclization protocol in which five new stereocenters were set with exceptional stereocontrol. Application of this strategy in the transannular manifold to a total synthesis of (−)-spinosyn A will be reported in due course.

Acknowledgment. Financial support provided by the National Institutes of Health (GM 26782) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for intermediates **10**, **14,** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678. (b) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.