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Exploring the Original Proposed Biosynthesis of (+)-Symbioimine: Remote Exocyclic Stereocontrol in a Type I IMDA Reaction

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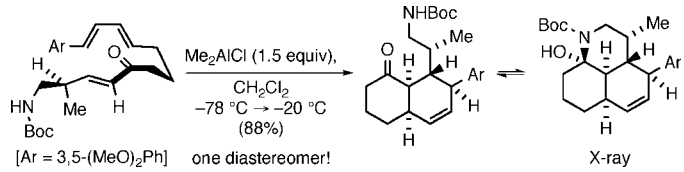
ABSTRACT



The originally proposed biosynthesis of (+)-symbioimine was explored, resulting in the successful intramolecular Diels−Alder (IMDA) cyclization of an appropriate (*E*,*E*,*E*)-1,7,9-decatrien-3-one. In contrast to the originally proposed biosynthesis, the IMDA reaction appears to proceed via an *endo* transition state. Remarkably, a single exocyclic stereogenic center effectively controls the π-facial selectivity affording a highly diastereoselective cycloaddition.

In 2004, Uemura and co-workers reported the isolation of (+)-symbioimine (**1**) from a dinoflagellate *Symbiodinium* sp. living symbiotically in the marine flatworm *Amphiscolops* sp.[1] In addition to its unique structural features (e.g., a zwitterionic iminium sulfate and a compact tricyclic core containing five contiguous stereocenters), (+)-**1** demonstrated promising inhibitory activity against the RANKL-induced differentiation of murine RAW264 hematopoietic precursor cells into osteoclasts without affecting overall cell viability. This antiosteoclastogenic activity marked (+)-**1** as a possible entry point into a new small-molecule-based modality for osteoporosis.[2] Accordingly, several research groups have reported efforts toward symbioimine[3] and related compounds,[4] including both racemic[3a,c] and enantioselective total syntheses.[3e] In the original isolation report, the authors proposed a biosynthesis involving a tandem diastereoselective *exo* intramolecular Diels−Alder (IMDA) cycloaddition/imine condensation of (*E*)-enone **2** (Scheme 1).[1a] This proposed type I IMDA cyclization is remarkable in at least two aspects. First, the preponderance of literature precedents indicates that

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(1) (a) Kita, M.; Kondo, M.; Koyama, T.; Yamada, K.; Matsumoto, T.; Lee, K.; Woo, J.; Uemura, D. *J. Am. Chem. Soc.* **2004**, *125*, 4794. (b) Kita, M.; Ohishi, N.; Washida, K.; Kondo, M.; Koyama, T.; Yamada, K.; Uemura, D. *Bioorg. Med. Chem.* **2005**, *13*, 5253.

(2) For other anti-osteoclastogenic natural products, see: (a) Hasegawa, S.-i.; Yonezawa, T.; Ahn, J.-Y.; Cha, B.-Y.; Teruya, T.; Takami, M.; Yagasaki, K.; Nagai, K.; Woo, J.-T. *Biol. Pharm. Bull.* **2010**, *33*, 487. (b) Kawatani, M.; Okumura, H.; Honda, K.; Kanoh, N.; Muroi, M.; Dohmae, N.; Takami, M.; Kitagawa, M.; Futamura, Y.; Imoto, M.; Osada, H. *Proc. Natl. Acad. Sci., U.S.A.* **2008**, *105*, 11691. (c) Li, J.-F.; Chen, S.-J.; Zhao, Y.; Li, J.-X. *Carb. Res.* **2009**, *344*, 599. (d) Cuong, N. X.; Minh, C. V.; Kiem, P. V.; Huong, H. T.; Ban, N. K.; Nhiem, N. X.; Tung, N. H.; Jung, J.-W.; Kim, H.-J.; Kim, S.-Y.; Kim, J.-A.; Kim, Y. H. *J. Nat. Prod.* **2009**, *72*, 1673. (e) Yoon, K. D.; Jeong, D. G.; Hwang, Y. H.; Ryu, J. M.; Kim, J. *J. Nat. Prod.* **2007**, *70*, 2029. (f) Lee, S.-Y.; Choi, D.-Y.; Woo, E.-R. *Arch. Pharm. Res.* **2005**, *28*, 909. (g) Park, C. K.; Kim, H. J.; Kwak, H. B.; Lee, T. H.; Bang, M.-H.; Kim, C. M.; Lee, Y.; Chung, D. K.; Baek, N.-I.; Kim, J.; Lee, Z. H.; Kim, H.-H. *Int. Immunopharm.* **2007**, *7*, 1507. (h) Kwak, H. B.; Lee, B. K.; Oh, J.; Yeon, J.-T.; Choi, S.-W.; Cho, H. J.; Lee, M. S.; Kim, J.-J.; Bae, J.-M.; Kim, S. H.; Kim, H. S. *Bone* **2010**, *46*, 724. (i) Ichikawa, H.; Murakami, A.; Aggarwal, B. B. *Mol. Cancer Res.* **2006**, *4*, 275.

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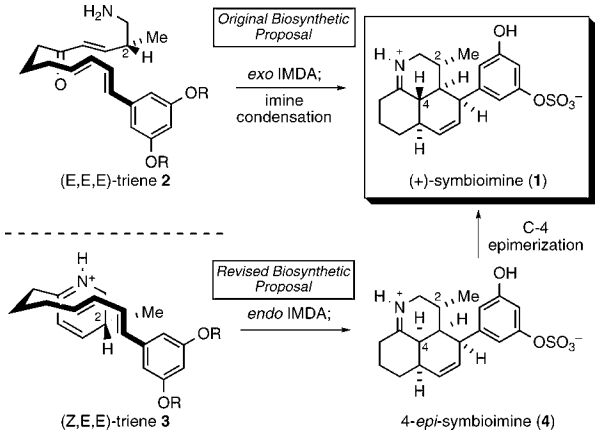
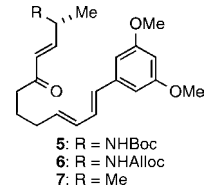
Scheme 1. Proposed Biosyntheses of (+)-Symbioimine (**1**)

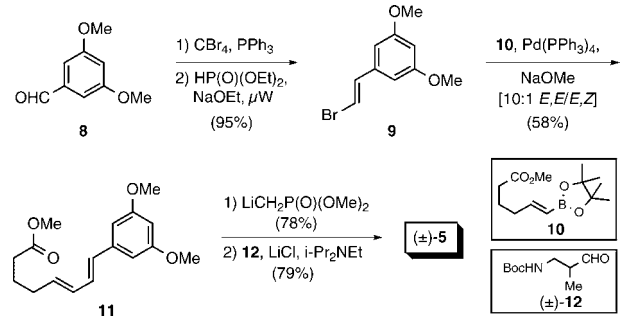


IMDA cycloadditions of (*E*,*E*,*E*)-1,7,9-decatrien-3-ones proceed prefentially through an *endo* and not *exo* transition state.[5] Second, the nonconstrained exocyclic C-2 stereocenter, which is decorated with two roughly equivalent substituents,[6] is tasked with controlling the π-facial selectivity for the cycloaddition. Perhaps in recognition of these unusual requirements, Uemura and co-workers later proposed an alternate biosynthesis involving a more traditional *endo* IMDA cyclization of dihydropyridinium **3** followed by epimerization of the relatively labile C-4 stereocenter to afford (+)-**1**.[1b] Snider[3c,d] and Thomson[3e] have both provided experimental support for this latter proposed biosynthetic pathway, in which the rotationally constrained C-2 stereocenter dictates the overall diastereoselectivity. Attempts to validate the originally proposed biosynthetic pathway (**2**→**1**), on the other hand, have not been successful. Maier reported that *N*-Boc triene **5** failed to undergo IMDA cycloaddition under thermal conditions (xylene, 180 °C).[3a] Similarly, Kobayashi reported that *N*-Alloc triene **6** and *E*-enone **7** both failed to undergo cyclization under either conventional heating (xylene, reflux, 2 d) or Lewis acid catalysis ($MeAlCl_2$, CH_2Cl_2, −78 °C).[3f,7] We report herein the first successful IMDA cycloaddition of (*E*)-enone (±)-**5**, resulting in the exclusive production of a single diastereomer in high yield. This product arises from an *endo* transition state, in contrast to the originally proposed *exo* transition state. Our results do lend support, however, to the unprecedented supposition that a freely rotating remote exocyclic stereocenter can effectively control π-facial selectivity in a type I IMDA process.



Synthesis of the requisite IMDA precursor (±)-**5** began with an efficient two-step conversion of 3,5-dimethoxybenzaldehyde (**8**) into (*E*)-vinyl bromide **9** (Scheme 2).[8]

Scheme 2. Synthesis of All-(*E*) Triene (±)-**5**



Coupling of bromide **9** with known boronate **10**[9] under standard Suzuki−Miyaura cross-coupling conditions[10] afforded diene **11** as an inseparable 10:1 ratio of (*E*,*E*) and (*E*,*Z*) olefin isomers, respectively. Addition of lithiated dimethyl methylphosphonate to methyl ester **11**, followed by Horner−Wadsworth−Emmons olefination[11] of the resultant β-ketophosphonate ester with *N*-Boc-β-alanal (±)-**12** afforded the desired (*E*)-enone (±)-**5** in 62% isolated yield over the two steps.

With (*E*,*E*,*E*)-triene (±)-**5** in hand, we next screened a battery of reaction conditions to induce the desired cycloaddition (Table 1). In agreement with previous reports,[3a,f] triene (±)-**5** failed to undergo IMDA reaction under thermal conditions (entry 1). Similarly, treatment with a substoichiometric amount of relatively mild Lewis acids (entries 2−5) or an organocatalyst (entry 6) resulted in essentially no conversion. One exception is the combination of 20 mol % $Sc(OTf)_3$ in THF, which afforded quantitative removal of the *tert*-butyl carbamate group (**5**→**13**, entry 4). Treatment with either strongly ionic conditions (entry 7) or harsher Lewis acids (entries 8−14) resulted in either no conversion or complete decomposition of starting material. Gratifyingly, we discovered that treatment of (±)-**5** with a superstoichio-

(3) (a) Maier, M.; Varseev, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 4767. (b) Sakai, E.; Araki, K.; Takamura, H.; Uemura, D. *Tetrahedron Lett.* **2006**, *47*, 6343. (c) Zou, Y.; Che, Q.; Snider, B. B. *Org. Lett.* **2006**, *8*, 5605. (d) Snider, B. B.; Che, Q. *Angew. Chem., Int. Ed.* **2006**, *45*, 932. (e) Kim, J.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3104. (f) Born, S.; Bacani, G.; Olson, E. E.; Kobayashi, Y. *Synlett* **2008**, *18*, 2877. (g) Born, S.; Kobayashi, Y. *Synlett* **2008**, 2479.

(4) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2007**, *9*, 1461.

(5) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1992; Vol. 5, pp 513−550.

(6) The *A*-values for a methyl (CH_3) and an aminomethylene (CH_2NH_2) group are expected to differ by ≤0.05 kcal/mol. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1990; pp 690−700.

(7) Microwave irradiation in methanol (160 °C) did affect the quantitative conversion of (*E*)-enone **7** into a 3:1 ratio of the expected *endo* product and the desired *exo* cycloadduct, respectively.

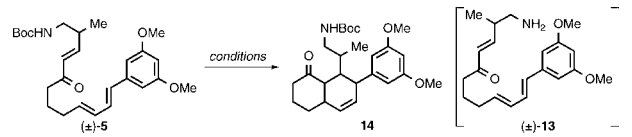
(8) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2002**, *58*, 1491.

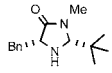
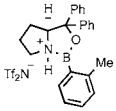
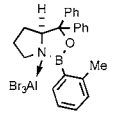
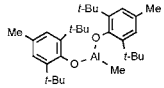
(9) Fujita, M.; Lee, H. J.; Okuyama, T. *Org. Lett.* **2006**, *8*, 1399.

(10) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

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

Table 1. IMDA Reaction Conditions



entry	reagent[a]	temp (°C)	time (h)	convn (%)[b]	product
1	heat	140[c]	3	0	—
2	$Yb(OTf)_3$[h]	23[d]	18	0	—
3	$Zn(OTf)_2$[h]	23[d]	18	0	—
4	$Sc(OTf)_3$[h]	23[e]	18	100	(±)-**13**
5	$Au(OAc)_3$[h]	23[e]	24	*trace*	(±)-**14**
6		23[f]	24	0	—
7	5.0M $LiClO_4$•Et_2O	23[g]	24	0	—
8		–20[d]	17	*trace*	(±)-**14**
9		–20[d]	22	0	—
10	BF_3•OEt_2[i]	–78 → 0[d]	2	100	*decomp*
11	BBr_3	–78 → 23[d]	5	100	*decomp*
12	$SnCl_4$	0[d]	12	100	*decomp*
13	$Ti(Oi\text{-}Pr)_4$[h]	23[d]	18	0	—
14		–78 → 23[d]	96	0	—
15	$MeAlCl_2$[j]	–78 → –20[d]	16	≥90	(±)-**14**
16	Me_2AlCl[j]	–78 → –20[d]	24	≥90	(±)-**14**
17	Me_2AlCl[j]	–78[d]	24	0	—

[a] Unless otherwise noted, 1 equiv of Lewis acid/catalyst was added. [b] Determined by TLC and ^1H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Solvent: $PhCH_3$. [d] Solvent: CH_2Cl_2. [e] Solvent: THF. [f] Solvent: CH_3CN. [g] Solvent: Et_2O. [h] 0.2 equiv. [i] 0.5 equiv. [j] 1.5 equiv.

metric amount (1.5 equiv) of either $MeAlCl_2$ or Me_2AlCl in CH_2Cl_2 at −20 °C led to the formation of a single cycloadduct (entries 15 and 16); less product decomposition was obtained employing the milder Lewis acid Me_2AlCl. Under optimized reaction conditions,[12] the resultant IMDA product (±)-**14** was isolated in 88% yield. Importantly, no reaction was observed when the mixture of (±)-**5** and Me_2AlCl was kept at −78 °C (entry 17), corroborating previous reports.[3f]

Characterization of the resultant IMDA product was complicated by its apparent interconversion between two discrete species on silica gel and in solution. X-ray crystallographic analysis of a single crystal obtained from MeOH unambiguously identified the major entity as the unsual *N*-Boc hemiaminal (±)-**14a** (Figure 1). With this lead, the

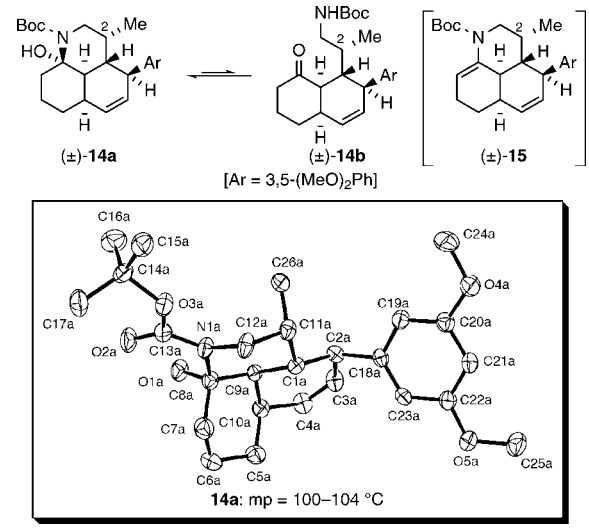


Figure 1. Product(s) from Me_2AlCl-induced IMDA of (±)-**5**, including ORTEP diagram (50% probability ellipsoids) of (±)-**14a**.

other species observed was deduced to be the corresponding ketone (±)-**14b**. With extended reaction times and/or when >1.5 equiv of Lewis acid was employed, enamine (±)-**15**, resulting from dehydration of hemiaminal (±)-**14a**, also was isolated in relatively small quantities. Importantly, all of the products possess the same relative stereochemistry, indicating that the exocyclic C-2 stereocenter enforced a level of π-facial selectivity for the [4 + 2] cycloaddition beyond the limits of detection for TLC analysis and NMR spectroscopy. *To the best of our knowledge, this represents the first example of such exquisite asymmetric induction by a single nonconstrained exocyclic stereocenter in a type I IMDA cycloaddition.*[5,13] On the basis of the observed diastereomer **14**, an *endo*-boat transition state model[14] can be proposed in which the C-2 stereocenter is oriented so as to minimize both intramolecular steric interactions with the approaching diene and $A_{1,3}$-strain with the dienophile C-4 proton (Figure 2). An alternative explanation to account for the remarkable π-facial selectivity is chelation of the Lewis acid by the ketone and *N*-Boc

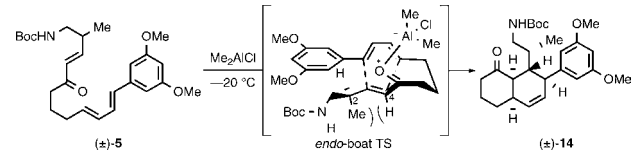


Figure 2. Model transition state for IMDA cyclization of **5**.

(12) 1.5 equiv Me_2AlCl (1.0 M in hexanes) was added to (±)-**5** in CH_2Cl_2 (0.1M) at −78 °C, held at that temperature for 1 h, and then stirred at −20 °C for 18h; see Supporting Information.

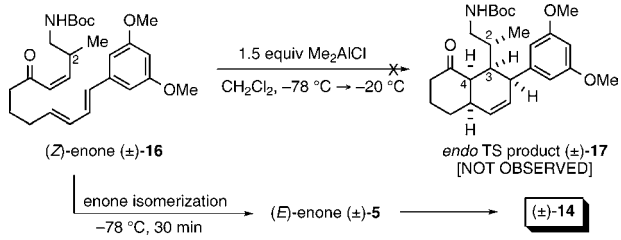
(13) In their synthesis of dihydrocompactin, Sammakia et al. reported a highly diastereoselective IMDA cyclization of a (*Z*,*E*,*E*)-1,7,9-decatrien-3-one in which a single exocyclic stereocenter effectively controls π-facial selectivity, but only *after* being constrained within a putative cyclic vinyloxocarbeneium ion. Sammakia, T.; Johns, D. M.; Kim, G.; Berliner, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 6504.

(14) While it is impossible to distinguish between the *endo*-chair and *endo*-boat transition states for our IMDA reaction, we favor the boat conformation based on compelling related studies by Roush. (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915. (b) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1355.

carbonyls, thus constraining the C-2 stereocenter within a strained 10-membered metallocycle.[15]

The resulting IMDA product (±)-**14** is doubly epimeric (C-4 and C-3) with the *exo*-transition state product originally proposed for the biosynthesis of (+)-**1**.[1a] Based on previous studies with related substrates,[3c−e] cyclization of (*Z*)-enone (±)-**16**[16] was expected to proceed via an *endo* transition state to provide *cis*-decalin (±)-**17**, which only differs from the symbioimine framework at the relatively acidic C-4 stereocenter (Scheme 3). Surprisingly, treatment of (*Z*,*E*,*E*)-triene

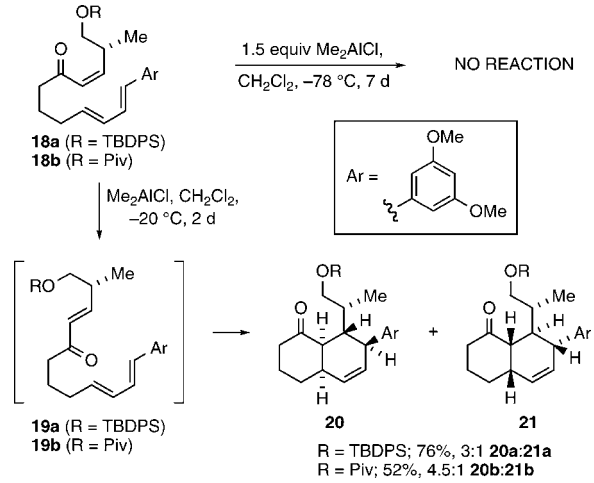
Scheme 3. Isomerization/IMDA Cyclization of (*Z*)-Enone **16**



(±)-**16** with Me_2AlCl produced cycloadduct (±)-**14** exclusively, indicating that enone isomerization was faster than IMDA cyclization. Indeed, (*Z*)-enone (±)-**16** completely isomerized to (*E*)-enone (±)-**5** within 30 min *at −78 °C* upon exposure to the Lewis acid.

To explore the role that the Boc-protected amine moiety in **16** and **14** plays in both the (*Z*)-to-(*E*) enone isomerization (e.g., **16**→**5**) and the remarkable π-facial selectivity upon IMDA cyclization, the corresponding TBDPS ether **18a** and pivalate ester **18b** were subjected to analogous Lewis acidic reaction conditions (Scheme 4).[17] Exposing (*Z*)-enone **18a** to Me_2AlCl at −78 °C resulted in no reaction after 7 days, indicating that exchange of the Boc-protected amine in (±)-**16** for a silyl ether significantly retards enone isomerization without affecting IMDA cyclization. Warming the reaction mixture to −20 °C, however, resulted in isomerization to the corrsponding (*E*)-enone **19a**,[18] followed by *endo*-IMDA cycloaddition to afford a 3:1 ratio of π-facial stereoisomers (+)-**20a** and (−)-**21a**, respectively, in 76% combined yield. The pivalate ester **18b** behaved similarly, providing a slightly improved ratio of diastereomers (4.5:1), albeit in lower

Scheme 4. Isomerization/IMDA Cyclization of (*Z*)-Enones **18**



overall yield. Under no circumstances did we isolate products arising from cyclization of the initial (*Z*)-enones **18a** or **18b**. In both cases, the observed π-facial selectively was significant but less than that observed for the cyclization of *N*-Boc-(*E*)-enone (±)-**5**. Notably, the relative stereochemistry of the major isomers (+)-**20a** and **20b** was identical to that present in cycloadduct (±)-**14**.

In summary, our studies confirm that the originally proposed biosynthesis of (+)-**1** involving an *exo*-IMDA cyclization of (*E*)-enone **2** is counter to the inherent reactivity of the all-*E* triene framework.[1a] When combined with previous studies by Snider[3c,d] and Thomson,[3e] our results also indicate the importance of constraining the corresponding (*Z*)-enone as a dihydropyridinium or related species, à la **3**, so as to increase the reactivity of the dienophile and to prevent facile enone isomerization. Most importantly, these studies provide compelling evidence that a single nonconstrained exocyclic stereocenter can adequately control π-facial selectivity in a type I IMDA cyclization of (*E*,*E*,*E*)-1,7,9-decatrien-3-ones. The resultant products (e.g., **14**, **15**, **20**, and **21**) will serve as synthetic precursors to epimeric analogues of (+)-**1**, valuable molecular tools for exploring the structure−activity relationship of the anti-osteoclastogenic alkaloid.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840.

(16) (*Z*)-Enone (±)-**16** was synthesized from methyl ester **11** using a modified Ando olefination protocol; see Supporting Information. (a) Touchard, F. P. *Eur. J. Org. Chem.* **2005**, *9*, 1790. (b) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105.

(17) Enantiopure (*Z*)-enones **18a** and **18b** were generated from methyl ester **11** and a homochiral terminal alkyne derived from (*S*)-(+)-Roche ester; see Supporting Information.

(18) The (*E*)-enones **19a** and **19b** were not isolated from the reaction mixtures but represent necessary intermediates for the observed products.