

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

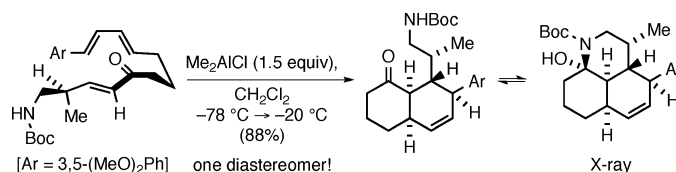
Jason P. Burke,[†] Michal Sabat,[†] Diana A. Iovan,[‡] William H. Myers,[‡] and Jason J. Chruma^{*,†}

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904, and
Department of Chemistry, University of Richmond, Richmond, Virginia 23173

jjc5p@virginia.edu

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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 symbioimine³ 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

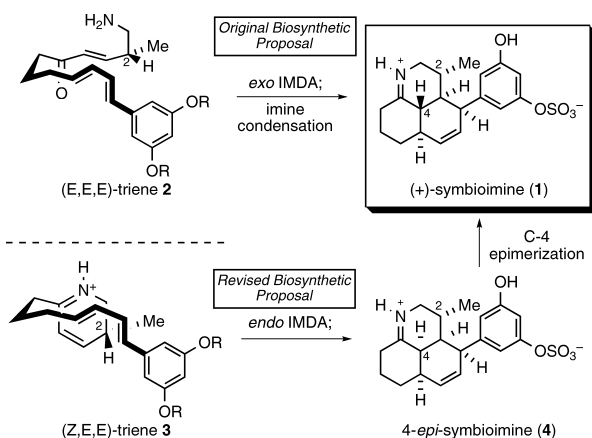
[†] University of Virginia.

[‡] University of Richmond.

(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.

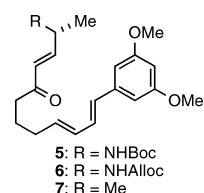
(2) For other anti-osteoclastogenic natural products, see: (a) Hasegawa, S.-i.; Yonezawa, T.; Ahn, J.-Y.; Cha, B.-Y.; Teruya, T.; Takami, M.; Yagasaki, K.; Nagai, K.; Woo, J.-T. *Biol. Pharm. Bull.* **2010**, *33*, 487. (b) Kawatani, M.; Okumura, H.; Honda, K.; Kanoh, N.; Muroi, M.; Dohmae, N.; Takami, 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.

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



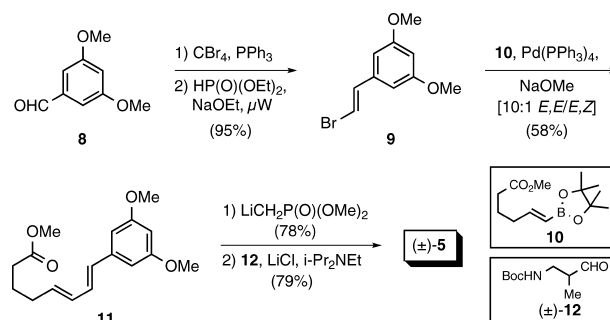
IMDA cycloadditions of (*E,E,E*)-1,7,9-decatrien-3-ones proceed preferentially through an *endo* and not *exo* transition state.⁵ Second, the nonconstrained exocyclic C-2 stereocenter, which is decorated with two roughly equivalent substituents,⁶ is tasked with controlling the π -facial selectivity for 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 (MeAlCl₂, CH₂Cl₂, -78 °C).^{3f,7} We report herein the first successful IMDA cycloaddition of (*E*)-enone (\pm)-**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 (\pm)-**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 (\pm)-5



Coupling of bromide **9** with known boronate **10**⁹ under standard Suzuki–Miyaura cross-coupling conditions¹⁰ 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 olefination¹¹ of the resultant β -ketophosphonate ester with *N*-Boc- β -alanine (\pm)-**12** afforded the desired (*E*)-enone (\pm)-**5** in 62% isolated yield over the two steps.

With (*E,E,E*)-triene (\pm)-**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 (\pm)-**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 (\pm)-**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 (CH₃) and an aminomethylene (CH₂NH₂) 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.

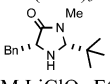
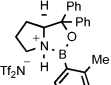
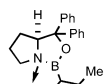
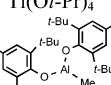
(8) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2002**, *58*, 1491.

(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.; Essendorf, 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 ₂ O	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-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 ₂ AlCl ^j	-78 → -20 ^d	24	≥90	(±)- 14
17	Me ₂ AlCl ^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: PhCH₃. ^d Solvent: CH₂Cl₂. ^e Solvent: THF. ^f Solvent: CH₃CN. ^g Solvent: Et₂O. ^h 0.2 equiv. ⁱ 0.5 equiv. ^j 1.5 equiv.

metric amount (1.5 equiv) of either MeAlCl₂ or Me₂AlCl in CH₂Cl₂ 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 Me₂AlCl. 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 Me₂AlCl 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

(12) 1.5 equiv Me₂AlCl (1.0 M in hexanes) was added to (±)-**5** in CH₂Cl₂ (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 vinyloxocarbenium 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.

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 unusual *N*-Boc hemiaminal (±)-**14a** (Figure 1). With this lead, the

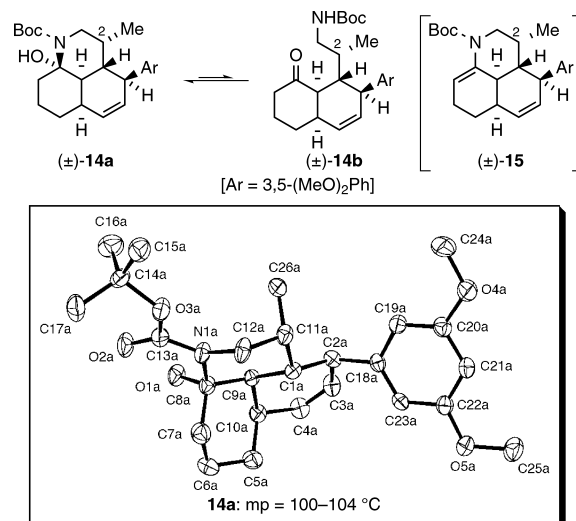


Figure 1. Product(s) from Me₂AlCl-induced IMDA of (±)-**5**, including ORTEP diagram (50% probability ellipsoids) of (±)-**14a**.

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 model¹⁴ 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

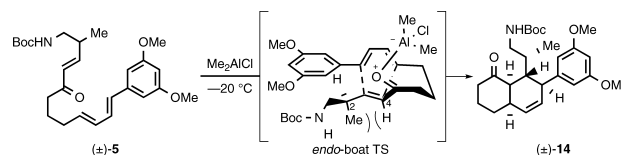
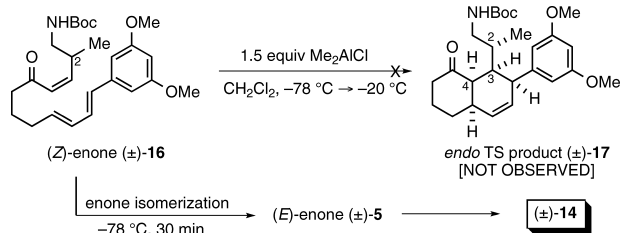


Figure 2. Model transition state for IMDA cyclization of **5**.

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

The resulting IMDA product (\pm)-**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 (\pm)-**16**¹⁶ was expected to proceed via an *endo* transition state to provide *cis*-decalin (\pm)-**17**, which only differs from the symbioimine framework at the relatively acidic C-4 stereocenter (Scheme 3). Surprisingly, treatment of (*Z,E,E*)-triene

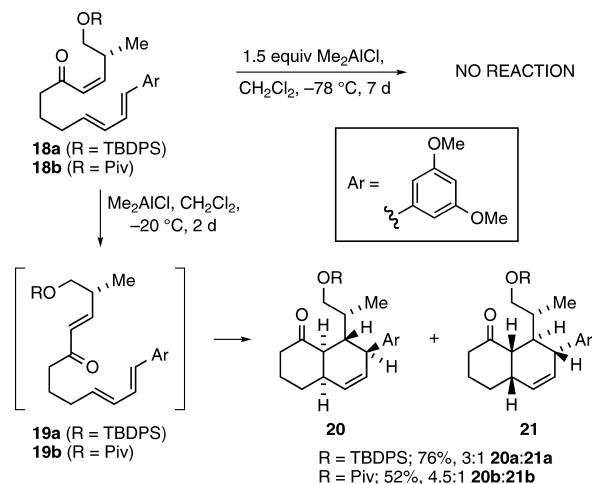
Scheme 3. Isomerization/IMDA Cyclization of (*Z*)-Enone **16**



(\pm)-**16** with Me_2AlCl produced cycloadduct (\pm)-**14** exclusively, indicating that enone isomerization was faster than IMDA cyclization. Indeed, (*Z*)-enone (\pm)-**16** completely isomerized to (*E*)-enone (\pm)-**5** within 30 min at $-78^\circ C$ 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 $-78^\circ C$ resulted in no reaction after 7 days, indicating that exchange of the Boc-protected amine in (\pm)-**16** for a silyl ether significantly retards enone isomerization without affecting IMDA cyclization. Warming the reaction mixture to $-20^\circ C$, however, resulted in isomerization to the corresponding (*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 selectivity was significant but less than that observed for the cyclization of *N*-Boc-(*E*)-enone (\pm)-**5**. Notably, the relative stereochemistry of the major isomers (+)-**20a** and **20b** was identical to that present in cycloadduct (\pm)-**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 (\pm)-**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.