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# Synthesis of 2-*epi*-Amphidinolide E: An Unexpected and Highly Selective C(2) Inversion during an Esterification Reaction

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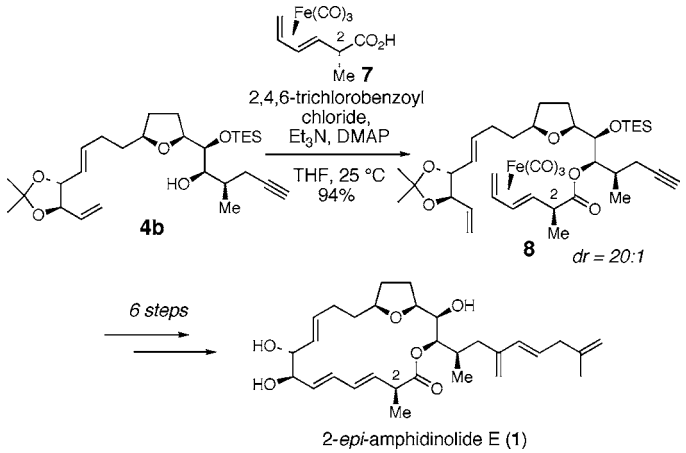
## ABSTRACT




**A synthesis of 2-*epi*-amphidinolide E (1) has been accomplished via an unexpected and highly diastereoselective C(2) stereochemical inversion during the modified Yamaguchi esterification of alcohol 4b and $Fe(CO)_3$-complexed dienoic acid 7.**

The amphidinolides are a family of structurally diverse macrolides isolated from the dinoflagellate *Amphidinium* sp, many of which display impressive anti-tumor activity.[1] As a consequence, the amphidinolides have attracted considerable interest as targets for synthesis and biological evaluation. Total syntheses of amphidinolides A,[2] J,[3] K,[4] P,[5] T,[6] W,[7] X,[8] and Y[9] have been reported.

Amphidinolide E[10] (**2**) is a 19-membered macrolactone featuring an embedded *cis*-tetrahydrofuran. While this structural motif is common within the amphidinolide family, the C(1)−C(6) α-chiral, $\beta,\gamma,\delta,\epsilon$-dienoate moiety of amphidinolide E is not found in any of the other amphidinolides. Amphidinolide E is cytotoxic to murine lymphoma L1210 and human epidermoid carcinoma KB cells, $IC_{50} = 2.0$ and 10.0 $\mu$g/mL, respectively.[1] Lee has reported the total synthesis of amphidinolide E.[11] Furthermore, Gurjar[12] and Marshall[13] have published studies toward amphidinolide E (**2**).

(1) For reviews on the amphidinolides: (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753. (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.*: *Anti-Cancer Agents* **2001**, *1*, 131. (c) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337. (d) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77.

(2) (a) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508. (b) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III *Org. Lett.* **2002**, *4*, 2841. (c) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. J.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420. (d) Trost, B. M.; Harrington, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 5028. (e) Trost, B. M.; Wrobleski, S. T.; Chisholm, J. D.; Harrington, P. E.; Jung, M. *J. Am. Chem. Soc.* **2005**, *127*, 13589. (f) Trost, B. M.; Harrington, P. E.; Chisholm, J. D.; Wrobleski, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 13598.

(3) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198.

(4) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765.

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We recently reported a total synthesis of amphidinolide E (**2**) via the ring-closing metathesis of polyene **3a** (Figure 1).[14]

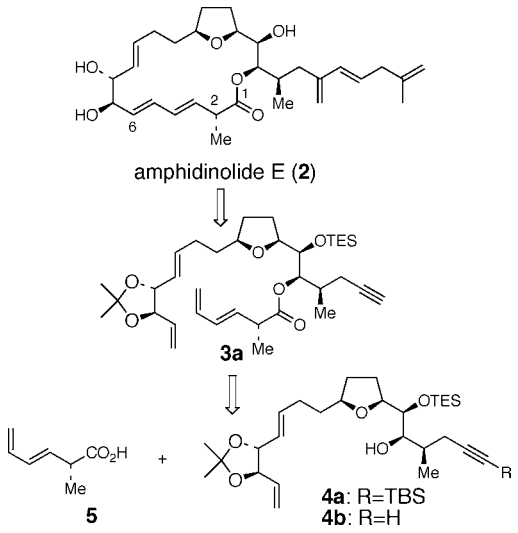
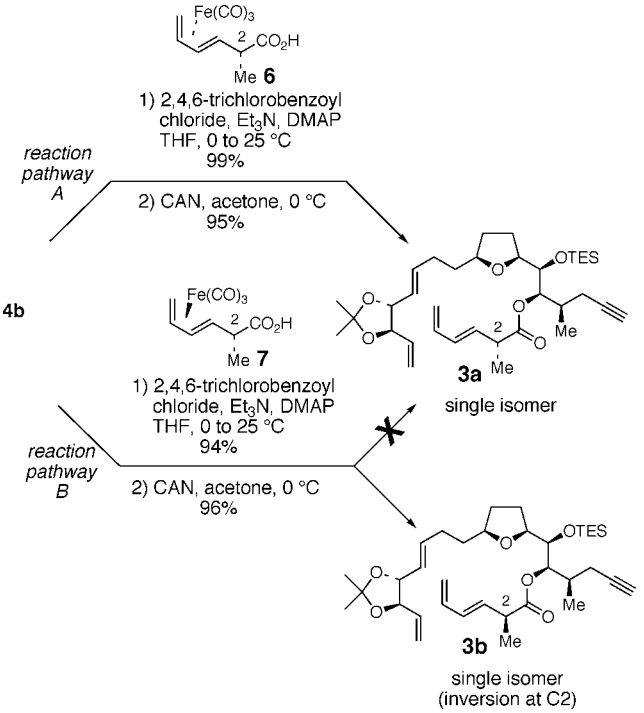



**Figure 1.** Strategy for the synthesis of amphidinolide E (**1**).

Installation of the C(1)−C(6) α-chiral, unconjugated dienoate via direct esterification of hindered alcohol **4a** (and closely related anologs) even in the presence of large excesses (10−20 equiv) of acid **5** proved to be extremely challenging. Only trace amounts of the corresponding ester were isolated under a variety of conditions. Furthermore, acid **5** was typically recovered as the fully conjugated, diene migrated carboxylic acid species.[14]

Ultimately, we found that use of $(CO)_3$Fe-complexed acid **6**,[14,15] a "diene protected" analogue of **5**, resulted in an efficient esterification of **4b** under the modified Yamaguchi conditions[16] (reaction pathway A, Scheme 1). Subsequent

**Scheme 1.** Divergent Reaction Pathways for Acids **6** and **7**




oxidative decomplexation afforded polyene **3a**, which was smoothly elaborated to amphidinolide E.

Surprisingly, when acid **7**, the $(CO)_3$Fe-diene diastereomer of **6**, was used in the same esterification−decomplexation sequence, polyene **3a** was not observed (reaction pathway B, Scheme 1). Instead, a product (**3b**) with a very similar $^1$H NMR spectrum to polyene **3a** was isolated. It was subsequently determined that this product was the C(2) stereochemically inverted isomer of **3a**, namely polyene **3b**.[17]

The stereochemical assignment of C(2) of **3b** was made on the basis of the data summarized in Table 1. Compounds **6**, **7**, **8**, and **9** were transformed into diene **10**, whose optical rotations were compared with material independently synthesized from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate.[18] Esters **8** and **9** are the immediate precursors of **3a** and **3b**, respectively. The C(2) stereochemistry of acids **6** and **7** was verified to be *2S* before being subjected to the esterification reaction (entries 1 and 2, Table 1). Furthermore, the *2S* stereochemistry was

(5) (a) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945. (b) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618. (c) Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921.

(6) (a) Fürstner, A.; Aissa, C.; Riveiros, R.; Ragot, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4763. (b) Aiessa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512. (c) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374. (d) Ghosh, A. K.; Liu, C. *Strategies Tactics Org. Synth.* **2004**, *5*, 255. (e) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998. (f) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297. (g) O'Brien, K. C.; Colby, E. A.; Jamison, T. F. *Tetrahedron* **2005**, *61*, 6243. (h) Deng, L.-S.; Huang, X.-P.; Zhao, G. *J. Org. Chem.* **2006**, *71*, 4625.

(7) (a) Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704. (b) Ghosh, A. K.; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085.

(8) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970.

(9) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194.

(10) (a) Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421. (b) Kubota, T.; Tsuda, M.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 1651.

(11) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*. ASAP.

(12) Gurjar, M. K.; Mohapatra, S.; Phalgune, U. D.; Puranik, V. G.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 7899.

(13) Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett.* **2005**, *7*, 5331.

(14) Va, P.; Roush, W. R. *J. Am. Chem. Soc.*, published online Nov. 30, http://dx.doi.org/10.1021/ja066663j.

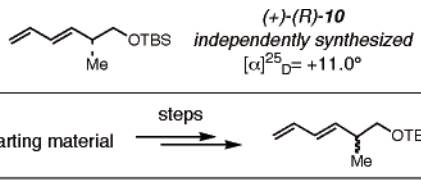
(15) (a) Donaldson, W. A.; Craig, R.; Spanton, S. *Tetrahedron Lett.* **1992**, *33*, 3967 (b) Wasicak, J. T.; Craig, R. A.; Henry, R.; Dasgupta, B.; Li, H.; Donaldson, W. A. *Tetrahedron* **1997**, *53*, 4185.

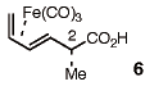
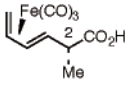
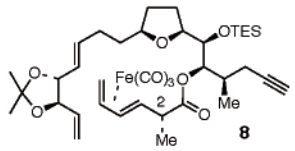
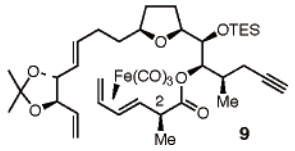
(16) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.

(17) Chronologically, polyene **3b** was synthesized prior to **3a** and was elaborated to 2-*epi*-amphidinolide E. We initially suspected that the stereochemistry of natural amphidinolide E may have been misassigned. It ultimately became apparent that a stereochemical inversion had occurred at C(2) in the esterification of **4b** and **7** after we repeated Kobayashi's stereochemical assignments for amphidinolide E by using advanced intermediates such as **11** as correlation compounds. Details of these stereochemical assignments will be reported in a full paper.

(18) Diene **10** was independently synthesized in 5 steps from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate, see the Supporting Information.

**Table 1.** Stereochemical Correlations Implicating Inversion at C(2) during the Esterification Reaction Leading to **3b** (via **9**)[a]



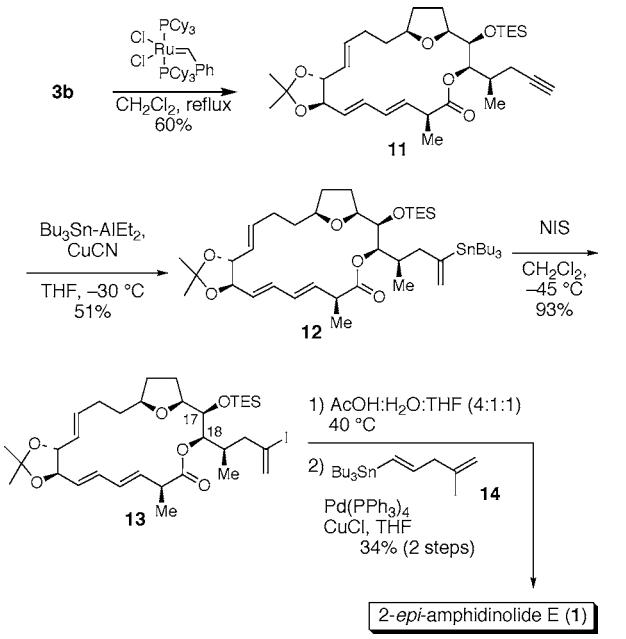

| entry | starting material | steps | overall yield | product [(+)- or (-)-10] |
|---|---|---|---|---|
| 1 |  **6** | A | 84% | (+)-(*R*)-**10** |
| 2 |  **7** | A | 68% | (+)-(*R*)-**10** |
| 3 |  **8** | B | 56% | (+)-(*R*)-**10** |
| 4 |  **9** | B | 61% | (–)-(*S*)-**10** |

[a] Step A: (1) $BH_3$·DMS, THF; (2) TBSCl, imidazole, $CH_2Cl_2$; (3) CAN, acetone, 0 °C. Step B: (1) DIBAL, MePh, −78 °C; (2) TBSCl, imidazole, $CH_2Cl_2$; (3) CAN, acetone, 0 °C

confirmed for amphidinolide E precursor **8** (prepared via the esterification reaction of **4b** with acid **6**, entry 3, Table 1).[14] On the other hand, the data in entry 4 leave no doubt that inversion at C2 occurs when acid **7** is used in the esterification reaction of **4b** (entry 4, Table 1).

Closure of the 19-membered macrocycle in **11** was accomplished in 60% yield via ring-closing metathesis with 20 mol % of Grubbs' first generation catalyst (Scheme 2). In addition, an inseparable mixture of enyne metathesis products was also isolated in 15% yield. Use of Grubbs' second generation[19] or the Grubbs−Hoveyda[19] catalysts resulted in only trace amounts of macrocycle **11** and significant decomposition of polyene **3b**. Stannylalumination−protonolysis[20] of alkyne **11** afforded vinylstannane **12** (51% yield). Treatment of vinylstannane **12** with *N*-iodosuccinimide yielded vinyl iodide **13** (93% yield). Acidic hydrolysis of the triethylsilyl ether and acetonide protecting groups in **13** afforded an inseparable 10:1 mixture of the desired C(18) and undesired C(17) lactone regioisomers. This is in contrast with our synthesis of amphidinolide E, in which case the analogous deprotection step provided only the 19-membered lactone.[14] Stille[21] cross coupling of the crude mixture of vinyl iodides with vinylstannane **14**[12] followed

**Scheme 2.** Completion of Synthesis of 2-*epi*-Amphidinolide E (**1**)




by HPLC purification afforded 2-*epi*-amphidinolide E in 34% yield from **13**. Biological data for 2-*epi*-amphidinolide E will be reported in due course.

The striking diastereoselectivity (dr = 20:1) for the formation of the C(2)-epimers of **8** and **9** prompted further studies to discern the role, if any, that the alcohol plays in influencing the diastereoselectivity of these esterification reactions. Table 2 summarizes the diastereoselectivites and yields obtained for the esterification reactions of three different alcohols with acids **6** and **7**. Esterification of the sterically unhindered, primary alcohol 3-phenylpropanol afforded a 1:1 C(2)-diastereomeric mixture with both acids **6** and **7** (entries 1 and 2, Table 2).[22] In contrast, esterification of the hindered primary alcohol, 2,2-dimethylpropanol, with acid **6** yielded a single isomer **17**,[23] but a 1:1 mixture of *ent*-**17** and **18** was obtained when acid **7** was used (entries 3 and 4).[22] Interestingly, coupling of 3-pentanol and acid **7** afforded a 5:1 mixure favoring **20** (entry 6), whereas **19**[25] was obtained exclusively from the coupling of **6** and 3-pentanol (entry 5). *Ester **20** is the enantiomer of **19**, and can be obtained only if inversion of C(2) of **7** occurs during the esterification reaction.*

We hypothesize that ketene intermediates may be involved in these esterification reactions (Figure 2). Ketenes are known to be generated from active ester intermediates in esterifi-

(19) For reviews of olefin metathesis: (a) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(20) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064.

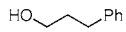
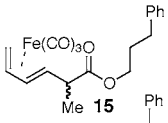
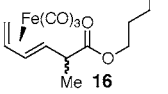
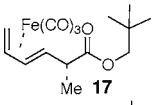
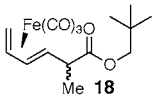
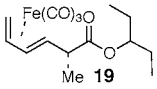
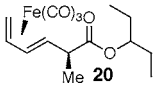
(21) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(22) A 1:1 mixture of C(2)-epimers was also obtained in the esterification of 3-phenylpropanol and acid **6** with EDCI·MeI and DMAP in $CH_2Cl_2$. The reaction does not proceed without DMAP.

(23) The C(2) stereochemistry of **17** and **19** was confirmed via a 3-step transformation to (+)-(*R*)-**10**: (1) DIBAL, MePh, −78 °C; (2) TBSCl, imidazole, $CH_2Cl_2$; (3) CAN, acetone, 0 °C.

(24) (a) Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733. (b) Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002**, *67*, 8975.

**Table 2.** Esterification Reactions of Acids **6** and **7** with Primary and Secondary Alcohols[a]

| entry | alcohol | acid | product | dr | % yield |
|---|---|---|---|---|---|
| 1 |  | **6** |  | 1:1 | 99% |
| 2 | | **7** |  | 1:1 | 99% |
| 3 |  | **6** |  | >20:1 | 79% |
| 4 | | **7** |  | 1:1 | 69% |
| 5 |  | **6** |  | >20:1 | 99% |
| 6 | | **7** |  | 5:1 | 99% |

[a] Esterification conditions: alcohol (1 equiv), acid (1.3 equiv), 2,4,6-trichlorobenzoyl chloride, $Et_3N$, DMAP, THF, 0 to 25 °C.

cations of carboxylic acids with acidic α protons.[24] Subsequent addition of the alcohol to ketene **22** and reformation of the C(2) stereocenter may occur diastereoselectively via protonation anti to the $(CO)_3Fe$ unit in the lowest energy conformation **23**. Alternatively, DMAP could add to the ketene intermediate.[25] Subsequent diastereoselective protonation of the enolate **24** by ROH would provide the acyl pyridinium salt **25**.

The rate of ketene formation could well be different for the two epimeric $Fe(CO)_3$ complexed dienoic acids **6** and **7**. In addition, unhindered alcohols (e.g., 3-phenylpropanol) could react with the active ester intermediates generated from **6** and **7** at rates competitive with ketene formation. Consequently, high diastereoselectivity is realized in these esterification reactions only with hindered, less reactive secondary alcohols (e.g., **4b** and 3-pentanol) for which the rate of direct esterification from the initially formed active ester intermediate is substantially slower than the rates of ketene formation from **6** and **7**.

An alternative mechanism is also plausible based on the work of Donaldson.[15] Donaldson has demonstrated that the methyl ester corresponding to **7** rapidly epimerizes under basic conditions, with an equilibrium ratio of approximately 1.4:1 at C(2). Donaldson also demonstrated that the diastereomeric methyl ester **21** (R = Me) undergoes hydrolysis faster than the methyl ester of **7**.[15] Accordingly, it is conceivable that a rapid C(2) epimerization of the active esters generated from **6** and **7** followed by dynamic kinetic resolution of this mixture could also play a role in some of the reactions reported herein. However, the fact that both **6** and **7** display C(2) epimerization without significant asymmetric induction in esterification with simple alcohols (e.g., Table 2, entries 1, 2, and 4), and the fact that **6** and **7** display strikingly different behavior in esterication reactions with neopentanol (entries 6 and 7), leads us to favor the ketene reaction pathway in competition with direct esterification of the active ester intermediates (but without dynamic resolution) to rationalize the stereoselectivity observed in these reactions, and especially in those cases that proceed with excellent asymmetric induction (e.g., **8** and **9**, and entries 3, 5, and 6 of Table 2).

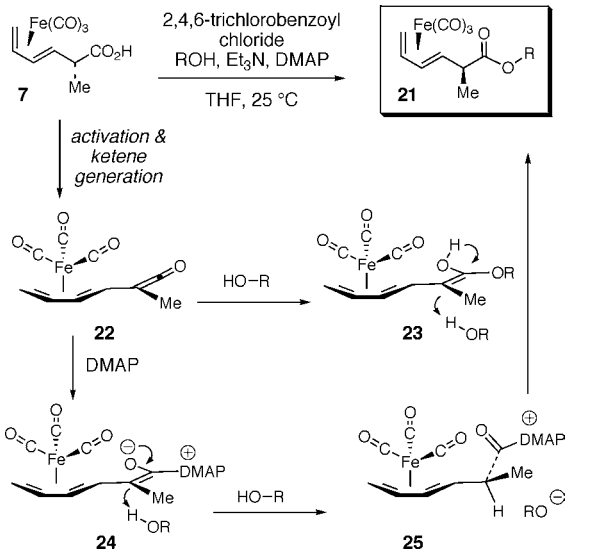



**Figure 2.** Proposed esterification pathway.

In summary, we have synthesized 2-*epi*-amphidinolide E via an unexpected and highly diastereoselective C(2) stereochemical inversion that occurs during the modified Yamaguchi esterification reaction of **4b** and **7**. A mechanistic rationale is presented that implicates diastereoselective protonation of enol (**23**) or enolate (**24**) intermediates derived from addition of the alcohol to the ketene intermediate **22**.

**Acknowledgment.** This work was supported by the National Institutes of Health (GM 38436).

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

OL0628098

(25) (a) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637 (b) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176.