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Asymmetric Catalysis Route to *anti*,*anti* Stereotriads, Illustrated by Applications

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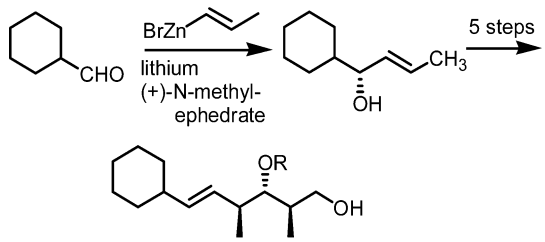
ABSTRACT



versatile *anti, anti* stereotriad building block

A short sequence based on asymmetric catalysis, chirality transfer, and an optimized carbometallation protocol gave an *anti*,*anti* stereotriad building block in six steps. Both enantiomers of the chirality source, *N*-methyl ephedrine, are inexpensive, and the auxiliary is recoverable. In one chiral series, the building block was converted to the "B-2" intermediate in Miyashita's synthesis of scytophycin C; in the enantiomeric series, it was converted to a key intermediate for aplyronine A and to the polyketide "cap" for the callipeltins.

As new and promising polypropionate antibiotics are discovered in nature, interest in these compounds as biological probes and as potential therapeutics continues to expand. The preparation of polypropionates is a challenge that has been met by the development of a variety of new methodologies. Nonetheless, the complexity of many target structures is such that more efficient syntheses from inexpensive materials are needed.

The *anti*,*anti* stereotriad is a noticeable feature of the structures of numerous polyketide antibiotics. Among these are macrolides isolated from aquatic organisms, primarily from marine sponges (e.g., swinholides) but also from sea snails (aplyronines, e.g., aplyronine A, **1a**) and fresh water cyanobacteria (scytophycins, e.g., scytophycin C, **1b**),[1] that bear a stereochemically rich, *N*-vinyl formamide-terminated side chain. There is speculation that the compounds isolated from the higher marine organisms are, in fact, the metabolites of cyanobacteria that are symbiotic with the hosts.[2] These marine macrolides alter the dynamics of the actin polymerization/depolymerization process by binding globular (monomeric) actin (G-actin) and by severing filamentous actin (F-actin). Perhaps, at least in part, because their action interferes with cell division,[3] these compounds are highly cytotoxic.

The *anti*,*anti* stereotriad is also found in a second class of marine natural products, the callipeltins. These cyclic and acyclic peptides are notable for their unusual amino acid residues as well as for their impressive biological activities.

(1) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237.

(2) (a) Andrianasolo, E. H.; Gross, H.; Goeger, D.; Musafija-Girt, M.; McPhail, K.; Leal, R. M.; Mooberry, S. L.; Gerwick, W. H. *Org. Lett.* **2005**, 7, 1375 and references therein. (b) Luesch, H.; Harrigan, G. G.; Goetz, G.; Horgen, F. D. *Curr. Med. Chem.* **2002**, *9*, 1791.

(3) Recent data suggest, however, that toxicity is not directly correlated with depolymerizing activity; see: (a) Suenaga, K.; Kimura, T.; Kuroda, T.; Matsui, K.; Miya, S.; Kuribayashi, S.; Sakakura, A.; Kigoshi, H. *Tetrahedron* **2006**, 62, 8278 and references therein. (b) Ojika, M.; Kigoshi, H.; Yoshida, Y.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Arakawa, M.; Ekimoto, H.; Yamada, K. *Tetrahedron* **2007**, *63*, 3138. (c) Also of interest in this context: Fuerstner, A.; Nagano, T.; Mueller, C.; Seidel, G.; Mueller, O. *Chem. Eur. J.* **2007**, *13*, 1452.

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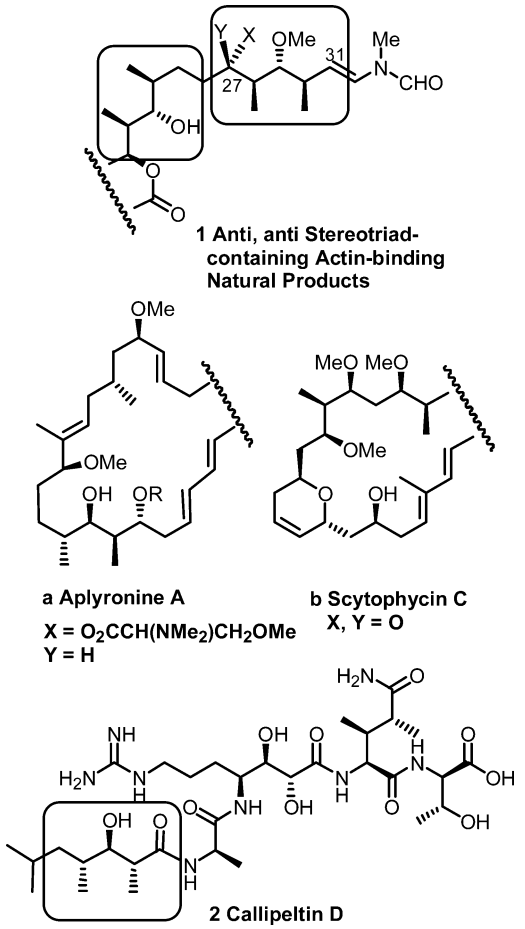
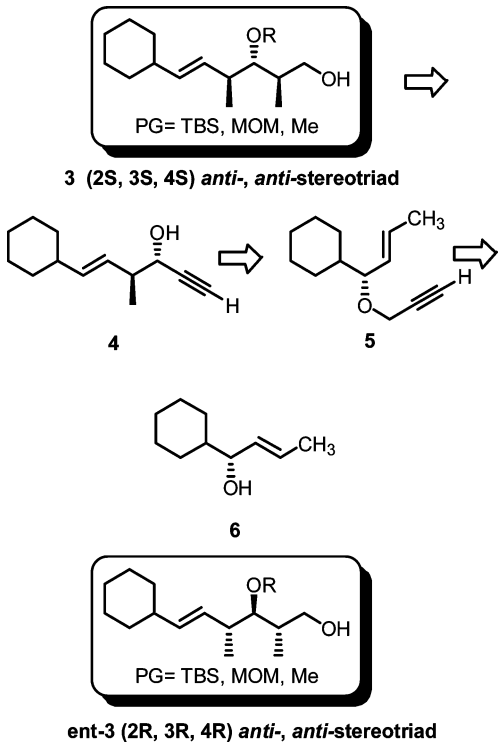


Figure 1. *anti*,*anti* Stereotriads in selected natural products.

In callipeltins A, C, D (**2**), and F-L from *Callipelta* sp. and *Latrunculia* sp.,[4] and in the closely related neamphamide A from *Neamphius huxleyi*,[5] a (2*R*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid moiety acts as an N-terminal "cap" of the peptide chain.

In order to gain easy access to polypropionate-derived natural products, we have focused on the exploitation of the 2,3-Wittig rearrangement. In 2006, we described the stereoselective rearrangement of a methallyl ether of a chiral *cis* allylic alcohol to produce a *syn* stereodiad that was subsequently elaborated to *syn*,*anti* stereotriad intermediates for a discodermolide synthesis.[6] The corresponding *anti* stereodiad is not cleanly available by variations of this direct approach; however, an *anti* stereodiad is available by the Wittig rearrangement of a *propargyl* ether of a *trans* allylic alcohol.[7] Therefore we considered the possibility that the *anti*,*anti* stereotriad equivalent **3** might be elaborated from propargyl ether **5** by way of the rearrangement product **4**.

Scheme 1. Enantiomeric Stereotriad Building Block Targets and Retrosynthetic Postulate



This approach to the *anti*,*anti* stereotriad **3** offered two desirable features. First, the precursor of the Wittig rearrangement substrate, chiral alcohol **6**, should be available by an asymmetric addition reaction in which the chiral ligand can be easily recovered. Second, the enantiomeric stereotriad **ent-3** should be equally available by applying the same approach in the enantiomeric series.

The practicality of our overall strategy and its utility have now been demonstrated by the facile preparation of Miyashita's "B-2" (**7**), a building block in the synthesis of scytophycin C (**1b**);[8,9] aldehyde **8**, an intermediate in Paterson's approach to aplyronine A (**1a**); and the TBS-protected (for use in total synthesis) 3-hydroxy-2,4,6-trimethylheptanoic acid **9** (TBS-Htmha), the "cap" for callipeltins (e.g., **2**).[10]

(4) D'Auria, M. V.; Sepe, V.; D'Orsi, R.; Bellotta, F.; Debitus, C.; Zampella, A. *Tetrahedron* **2007**, *63*, 131 and references therein. For the total synthesis of Callipeltin D, see Cranfill, D. C.; Morales-Ramos, A. I.; Lipton, M. A. *Org. Lett.* **2005**, *7*, 5881.

(5) Oku, N.; Gustafson, K. R.; Cartner, L. K.; Wilson, J. A.; Shigematsu, N.; Hess, S.; Pannell, L. K.; Boyd, M. R.; McMahon, J. B. *J. Nat. Prod.* **2004**, *67*, 1407.

(6) Parker, K. A.; Cao, H. *Org. Lett.* **2006**, *8*, 3541.

(7) Tsai, D. J. S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1842.

(8) For the structure determination and biological activities of scytophycin C, see: Smith, C. D.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Cancer Res.* **1993**, *53*, 1343.

(9) (a) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3579. (b) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3583. (c) A total synthesis of scytophycin C was also reported by Paterson, I.; Watson, C.; Yeung, K.-S.; Ward, R. A.; Wallace, P. A. *Tetrahedron* **1998**, *54*, 11955.

(10) (a) For an elegant and efficient synthesis of TBS-Htmha in which the source of chirality is pseudoephedrine was reported by Lipton, see: Turk, J. A.; Visbal, G. S.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 7841. (b) For an earlier synthesis of the *O*-benzyl-protected acid, see: Zampella, A.; D'Auria, M. V. *Tetrahedron: Asymm*etry **2002**, *13*, 1237. (c) For preparations of the (2*R*,3*R*,4*S*)-diastereomer, see: Zampella, A.; Sorgente, M.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2002**, *13*, 681. Guerlavais, V.; Carroll, P. J.; Joullie, M. M. *Tetrahedron: Asymmetry* **2002**, *13*, 675.

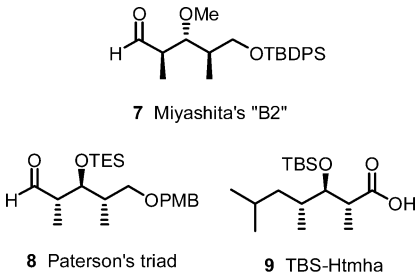
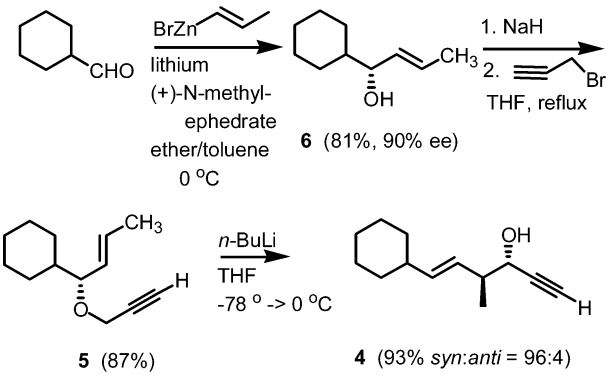


Figure 2. Illustrative targets.

Preparation of stereotriad building block **3** was to be based on elaboration of the 2,3-Wittig rearrangement product **4**. Synthesis of this key intermediate began (Scheme 2) with the addition of (*E*)-1-propenylzinc bromide to cyclohexanecarboxaldehyde in the presence of (+)-*N*-methylephedrine according to the method of Oppolzer.[11] Allylic alcohol **6** was obtained in 81% yield and 90% ee.[12] Alkylation with propargyl bromide afforded ether **5** in 87% yield. Application of standard [2,3]-Wittig rearrangement conditions afforded (*E*)-propargylic alcohol **4** (93% yield). The ratio of the *anti*/*syn* diastereomers in this rearrangement product was, as judged by integration of the ^{1}H NMR spectrum, 96:4.

Scheme 2. Three-Step Preparation of the Chiral *anti* Stereodiad



At this point, our plan was to convert alcohol **4** to the key intermediate **3** (R = Me) by a sequence consisting of carbometallation with a proton quench, O-methylation, and hydroboration (see Scheme 3). Efforts to obtain useful results by applying the Duboudin carbometallation protocol[13] to substrate **4** afforded a low yield of the desired α-adduct **10** along with the *β*-adduct and recovered starting material. In order to develop an efficient conversion of terminal propargyl alcohols to methallyl alcohols, we studied the product distribution of the carbometallation of 1-cyclohexyl-2-propyn-1-ol (Table 1).[14,15]

Scheme 3. Conversion of *anti* Stereodiad **4** to *anti*,*anti* Stereotriad **3** and Elaboration to Miyashita's "B-2" **7**

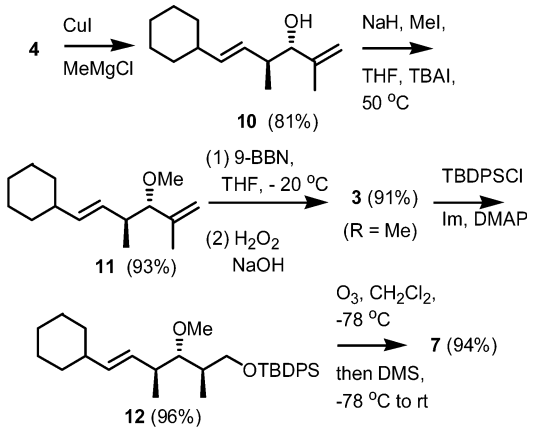


Table 1. Distribution of Starting Material (SM) and Products: CuI-Catalyzed Addition of Methylmagnesium Halide to 1-Cyclohexyl-2-propyn-1-ol

MeMgX X, equiv	CuI (equiv)	solvent	SM, α-adduct, *β*-adduct (%)
Br, 2.5	0.95	THF	54, 24, 22
Br, 4.0	2.0	THF	28, 58, 14
Br, 4.0	3.0	THF	62, 22, 16
Br, 4.0	2.0	Et_2O	65, 4, 31
Br, 4.0	2.0	dioxane	100, 0, 0
Cl, 4.0	2.0	THF	21, 79, trace
I, 4.0	2.0	THF	87, 13, trace

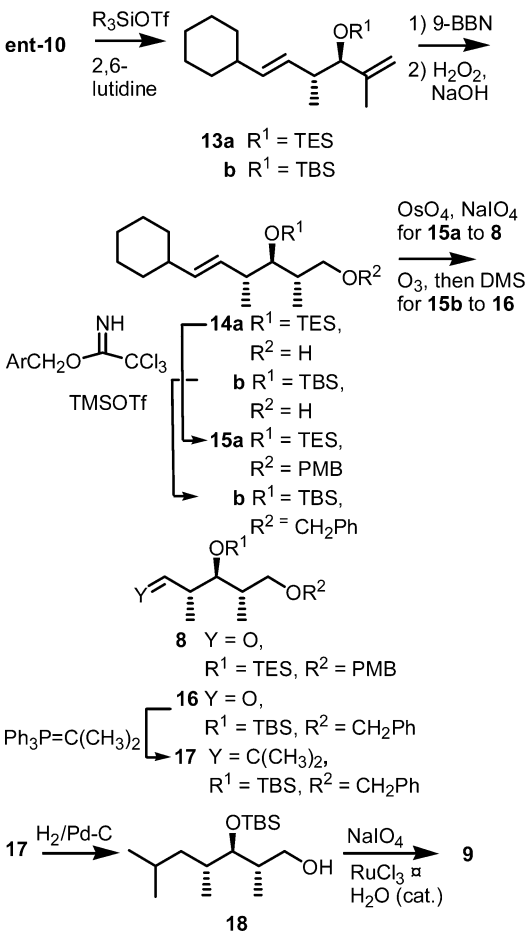
Application of the most favorable protocol to substrate **4** resulted in the isolation of an 81% yield of the desired alcohol **10** along with the recovery of some starting material. Methylation and hydroboration gave the desired synthon **3** (R = Me). Silylation and ozonolysis demonstrated its utility by conversion to the desired "B-2," aldehyde **7**.

An advantage of the asymmetric addition−rearrangement approach to stereotriad-containing intermediates is that both enantiomers of key compound **3** are readily available. For the preparation of Paterson's triad **8** or TBS-Htmha (**9**), it is more efficient to use a synthon derived from **ent-10** than one derived from the previously prepared **10**. Therefore the five-step asymmetric synthesis was applied in the enantiomeric series (**ent-6** → **ent-4** → **ent-10**, as in Schemes 2 and 3).

Both targets **8** and **9** were then prepared (Scheme 4). Conversion of **ent-10** to Paterson's triad **8** was accomplished

(11) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.
(12) The ee was determined by Mosher ester analysis; see Supporting Information. The chiral ligand was recovered quantitatively in purity that was appropriate for use in further reactions.
(13) (a) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1−11. (b) Duboudin, J. G.; Jousseaume, B. J.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227−232.
(14) Details will be reported in a full paper.
(15) During the course of our work, a similar study was reported for the carbometallation of terminal, secondary propargyl alcohols in which the substituent was a straight-chain alkyl group. See: Lu, Z.; Ma, S. *J. Org. Chem.* **2006**, *71*, 2655.

Scheme 4. Preparation of Paterson's Triad **8** and TBS-Htmha **9**



by silylation with TES triflate, hydroboration with 9-BBN (→ **14a**), and protection with *p*-methoxybenzyl trichloroacetamidate. Under standard ozonolysis conditions, olefin **15a** suffered oxidative removal of the PMB group as indicated by the appearance of *p*-methoxybenzaldehyde. However, a two-step procedure with OsO_4 and buffered $NaIO_4$ provided the aldehyde target **8**.[16] For elaboration of **ent-10** to the protected hydroxy trimethylheptanoic acid **9**, silylation with TBSOTf (→ **13b**) was followed by benzylation with benzyl trichloroacetimidate to give the fully protected olefin **15b**. Ozonolysis provided aldehyde **16** which was subjected to the Wittig reaction. Treatment of the trisubstituted olefin **17** with hydrogen in the presence of palladium on carbon effected both debenzylation and saturation of the double bond. Oxidation of primary alcohol **18**[17] gave TBS-Htmha (**9**).

The advantages of this approach to *anti,anti* stereotriad building blocks are (1) the use of asymmetric catalysis as a source of chirality, (2) the ready availability of catalysts for both chiral series, (3) the functional group pattern in the synthon (**3** or **ent-3**) itself, which allows generation of an aldehyde in one step in high yield, and (4) the relatively robust protocols required for the short scheme that provides synthon **3** or **ent-3**. More sophisticated applications are being pursued.

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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.

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(16) Paterson, I.; Blakey, S. B.; Cowden, C. J. *Tetrahedron Lett.* **2002**, *43*, 6005.

(17) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.