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Synthesis of a C20–C26 Segment of Superstolide A by Addition of a Chiral Allenylzinc Reagent to (*R*)-*N*-Boc Alaninal

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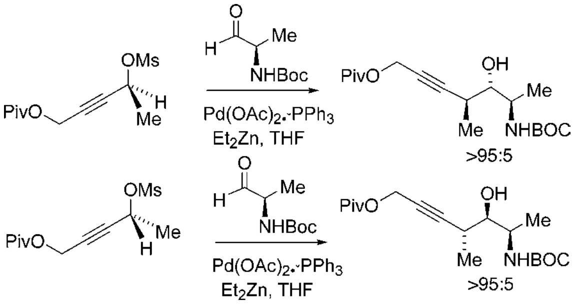
ABSTRACT



Additions of chiral allenylzinc and indium reagents to *N*-Boc alaninal were examined as a possible route to a C20–C26 segment of superstolide A. Allenylzinc reagents, prepared in situ by palladiozincation of (*R*)- and (*S*)-5-pivalyloxy-3-butyn-2-ol mesylate, showed excellent reagent control to afford the anti,syn and anti,anti diastereomers as the nearly exclusive adducts.

Superstolide A is a constituent of the deep-water marine sponge *Neosiphonia superstes*. This structurally novel macrolide, which shows nM activity against murine and human leukemia, colon, and nasopharyngeal cells,[1] has been the subject of several recent synthetic studies.

D'Auria and co-workers[2] reported a synthesis of the C21−C26 polyketide segment of superstolide A in which Brown's crotylborane reagents[3] played a major part. An analogous route to the C20−C26 segment has been reported by the groups of Roush[4] and Jin.[5] Roush has also assembled the hydronaphthalene segment (C7−C18) by means of an intramolecular Diels−Alder construct (Figure 1).[6] Our projected approach to superstolide A follows along similar lines except for the methodology used to assemble the C20−C26 polyketide segment **C**, in which chiral allenylmetal reagents play a major role. Such reagents have been found to react with chiral α-methyl and α-alkoxy aldehydes with excellent reagent control to afford key components of polyketide natural products.[7] For our planned synthesis of fragment **C**, the addition would involve a protected α-amino aldehyde, a

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[1] D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. *J. Am. Chem. Soc.* **1994**, *116*, 6658.

[2] Zampella, A.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2001**, *12*, 1543.

[3] Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

[4] Roush, W. R.; Hertel, L.; Schnaderbeck, M. J.; Yakelis, N. A. *Tetrahedron Lett.* **2002**, *43*, 4885. Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 3838.

[5] Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447.

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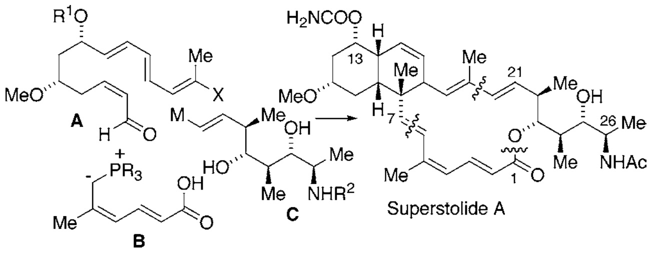
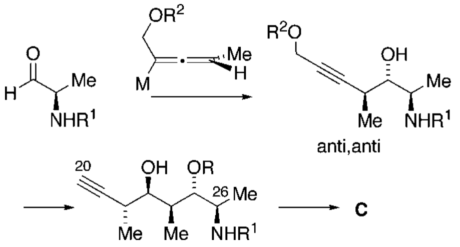


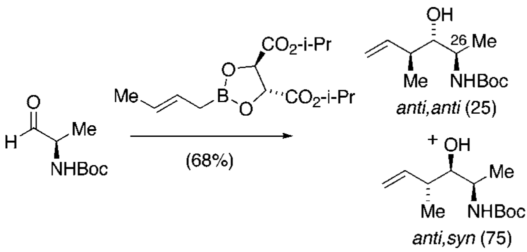
Figure 1. Synthetic plan for superstolide A.

class of substrates previously unexamined in these additions (eq 1).



(1)

We had reason to believe that, because of certain structural features, allenylmetal reagents might prove to be more selective than some of their allylmetal counterparts previously employed for this application. Particularly relevant are some earlier studies of Roush and co-workers who found that additions of a chiral crotylboronic tartrate reagent to (*R*)-*N*-Boc alaninal proceeds with unprecedented substrate control to afford the anti,syn adduct as the major product rather than the predicted reagent-controlled anti,anti isomer (eq 2).[4] Fortunately, Browns crotyl Ipc borane reagent overcame the substrate preference to yield the desired anti,anti adduct with high selectivity.[3]



(2)

The boronate finding called attention to the possibility that in additions of certain chiral allylmetal reagents to α-chiral aldehydes, the normally favored reaction pathway can be blocked by a 1,3-*syn*-pentane interaction that cannot be overcome by reagent control (Figure 2). Because of the linear arrangement of the allene moiety, these unfavorable interactions would not exist in analogous additions involving allenylmetal reagents. It therefore appeared likely that reactions of both enantiomers of chiral allenylmetal reagents with *N*-Boc alaninal and related aldehydes could proceed with reagent control, subject to the usual Felkin–Anh and chelation constraints of the aldehyde substrates.

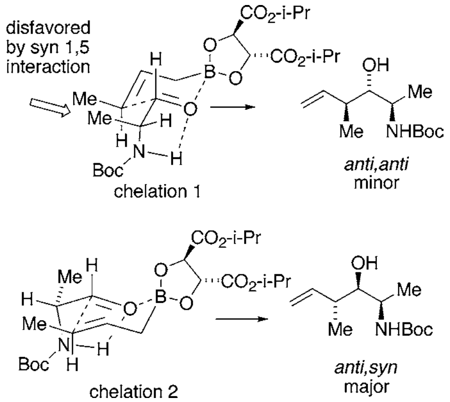


Figure 2. Substrate control in the addition of a chiral allylboronate reagent to *N*-Boc alaninal.

The expected outcomes of these additions are illustrated in Figure 3. Accordingly, approach of the (*P*)-allenylmetal reagent to the si face of the carbonyl of an H-bonded conformer is blocked by the α-methyl substituent of the alaninal (chelation 1). However, attack at the re face suffers from a more serious eclipsing interaction between the allenyl methyl and the aldehyde substituent (chelation 2 and anti-Felkin–Anh 1). Therefore, a reagent-controlled transition state (Felkin–Anh) involving a non-H-bonded aldehyde might reasonably be expected. Addition of the (*M*)-allenyl-

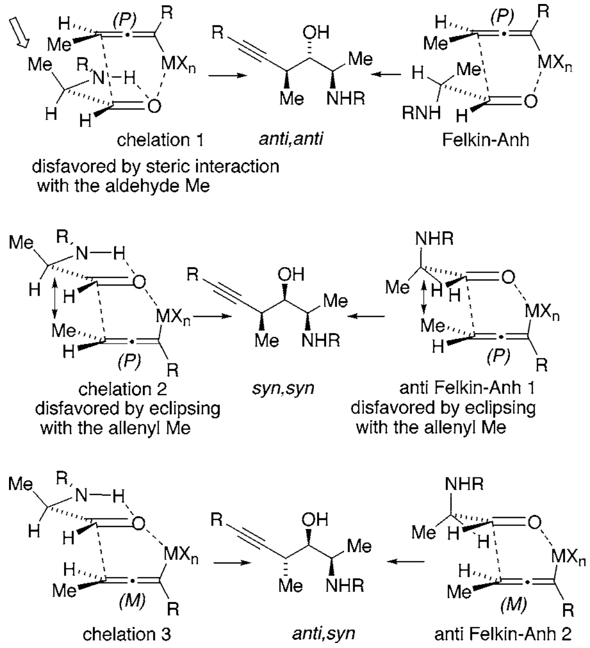
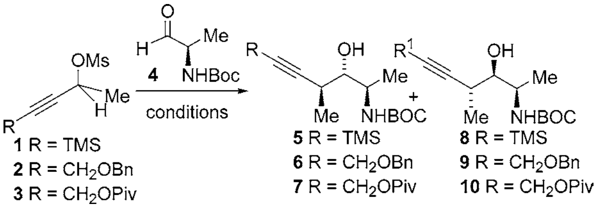


Figure 3. Pairing of (*P*)- and (*M*)-allenylmetal reagents with (*R*)-*N*-Boc alaninal.

metal reagent to an (*R*)-alaninal derivative, on the other hand, could proceed through a favored (matched) chelation transition state (chelation 3) or, possibly, anti-Felkin−Anh 2. The fourth possibility (not shown), which would afford the syn,-anti diastereomer, is disfavored by eclipsing of the allenyl methyl and the aldehyde substituent, in the manner of chelation 2 and anti-Felkin−Anh 1.

For our exploratory studies we selected the *N*-Boc derivative of (*R*)-alaninal **4** as the aldehyde substrate.[2] Allenylindium reagents, prepared in situ from propargylic mesylates, were examined first.[8] Addition of the racemic reagent (*RS*)-**1**, derived from the mesylate of 4-TMS-3-butyn-2-ol by palladioindation,[9] afforded a 1:1 mixture of anti,anti and anti,-syn adducts **5** and **8** (Table 1), indicative of a reaction with effectively no substrate control. In accord with this surmise, the (*P*)- and (*M*)-allenylindium reagents, prepared from the (*R*)- and (*S*)-TMSpropargylic mesylates (*R*)-**1** and (*S*)-**1**, afforded the anti,anti and anti,syn adducts with essentially complete stereoselectivity. The benzyloxymethyl-substituted propargylic mesylates (*RS*)-**2**, (*R*)-**2**, and (*S*)-**2** showed analogous selectivity. Surprisingly, the related racemic pivaloxymethyl counterpart (*RS*)-**3** gave no addition product; the starting aldehyde was recovered unchanged. However, when the InI component of this reaction was replaced by Et_2Zn, the two diastereomeric anti,anti adducts **7** and **10** were produced as a 1:1 mixture. The use of the (*R*)- and (*S*)-mesylates (*R*)-**3** and (**S**)-**3**, respectively, in this addition afforded the anti,anti and anti,syn adducts, as before, with virtually complete diastereoselectivity.

Table 1. Additions of Allenylzinc and Indium Reagents to *N*-Boc Alaninal[a]



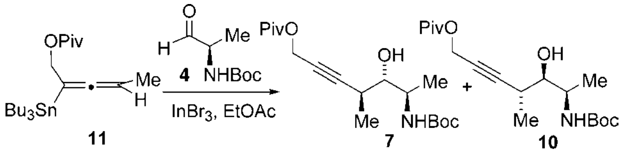
1 R = TMS
2 R = CH_2OBn
3 R = CH_2OPiv
5 R = TMS
6 R = CH_2OBn
7 R = CH_2OPiv
8 R = TMS
9 R = CH_2OBn
10 R = CH_2OPiv

R	conditions	configuration	yield (%)	anti,anti:anti,syn
TMS **1**	A	racemic	85	50:50
TMS **1**	A	(*R*)-	69	>95:5
TMS **1**	A	(*S*)-	74	<5:95
CH_2OBn **2**	A	racemic	85	50:50
CH_2OBn **2**	A	(*R*)-	80	>95:5
CH_2OBn **2**	A	(*S*)-	90	10:90
CH_2OPiv **3**	A	racemic	0	
CH_2OPiv **3**	B	racemic	70	50:50
CH_2OPiv **3**	B	(*R*)-	78	>95:5
CH_2OPiv **3**	B	(*S*)-	50	<5:95

[a] Key: A = $Pd(OAc)_2{\cdot}PPh_3$, InI, THF; B = $Pd(OAc)_2{\cdot}PPh_3$, Et_2Zn, THF.

We have previously employed a pivaloxymethyl indium bromide reagent for a diastereoselective addition reaction involving a chiral α-methyl-*β*-OTBS propanal with excellent results.[10] In that case the indium reagent was prepared by transmetalation of an allenylstannane precursor. Applying that protocol to aldehyde **4**, we prepared the racemic allenylindium bromide reagent in situ from the allenylstannane **11** (Table 2).

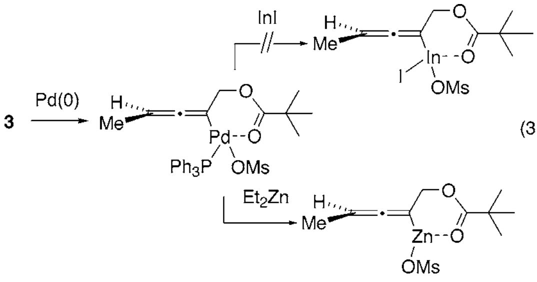
Table 2. Additions of Allenylindium Bromide Reagents to *N*-Boc Alaninal



configuration	yield (%)	anti,anti:anti,syn
racemic	71	40:60
(*P*)-	83	80:20
(*M*)-	80	5:95

This reaction led to a 40:60 mixture of anti,anti and anti,-syn adducts, indicative of a partial kinetic resolution. When these conditions were applied to the (*P*)-allenylstannane **11**, an 80:20 mixture of the two adducts was formed. As expected, the matched combination of aldehyde **4** and the (*M*)-stannane afforded the anti,syn adduct **10** as the nearly exclusive product.

The dramatic difference in reactivities of allenylindium reagents prepared from the alkynylTMS and CH_2-OBn mesylates **1** and **2** compared to that of the analogous reagent from the CH_2OPiv mesylate **3** may result from the ability of the latter to form an internally coordinated species, which inhibits oxidative transmetalation of the allenylpalladium precursor of the indium reagent (eq 3). That the effect is not related to the aldehyde substrate **4** was ascertained by unsuccessful attempts to effect addition of the putative indium reagent to isobutyraldehyde, which led to recovery of the starting material. Presumably, the analogous zinc transmetalation is less inhibited by internal chelation.



(3)

Conversion of the anti,anti adduct **7** to a suitable derivative of segment **C** for our projected superstolide synthesis was achieved by the sequence outlined in Scheme 1. Accordingly, acetonide formation, followed by reduction with Red-Al,

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(7) Marshall, J. A.; Ellis, K. C. *Org. Lett,* **2003**, *5*, 1729 and references therein.

(8) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

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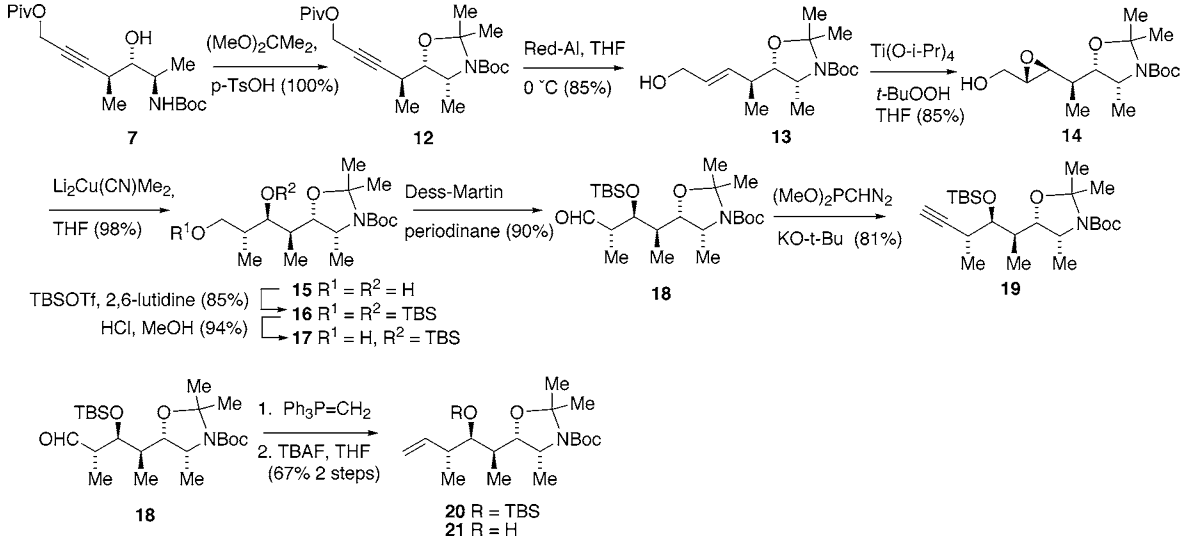
Scheme 1. Synthesis of a Possible Superstolide Precursor



afforded the allylic alcohol **13**. A matched Sharpless asymmetric epoxidation led to the epoxide **14**. This epoxide was also produced as the sole product in a substrate-directed reaction when the epoxidation was conducted in the absence of the tartrate ligand. Regioselective addition of a higher order methyl cyanocuprate reagent[11] effected conversion to the diol **15** in nearly quantitative yield. Silylation and selective desilyation, followed by Dess–Martin periodinane oxidation, afforded the aldehyde **18**, previously prepared by D'Auria[2] and Roush.[4] The spectral properties of this aldehyde were in accord with those reported. We also prepared the related alkene **20**, an intermediate in the superstolide fragment synthesis reported by Yakelis and Roush.[4] This was achieved through Wittig homologation of aldehyde **18**. The rotation and ^1H NMR spectrum of our material confirmed its identity. Furthermore, the derived alcohol **21**, a crystalline solid, exhibited an optical rotation and melting point coincident with the reported values.[4]

To complete the synthesis of an appropriate precursor to our intended superstolide intermediate **C**, we homologated aldehyde **18** with dimethyl (diazomethyl)phosphonate[12] whereupon the alkyne **19** was formed in high yield.

In addition to elaborating an efficient synthesis of a potential precursor of superstolide, these studies reveal a divergence in the palladiometalation route to allenylmetal reagents when the propargylic mesylate precursor possesses a ligating alkynyl substituent. Presumably, such substituents interfere with the transmetalation step of the sequence as (1) the analogous palladiozincation proceeds without incident and (2) a reactive allenylindium halide reagent can be prepared from such mesylates through use of an allenylstannane precursor.

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Supporting Information Available: Experimental procedures and ^1H NMR spectra for all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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