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(−)-Pseudodistomin E: First Asymmetric Synthesis and Absolute Configuration Assignment

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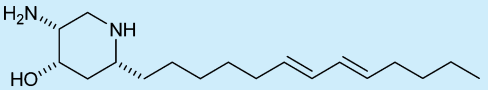
Supporting Information

ABSTRACT: (−)-Pseudodistomin E has been prepared for the first time, allowing its structure and absolute configuration to be confirmed. The established conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to methyl (*E*,*E*)-hepta-2,5-dienoate generated the C(2)-stereocenter, and iodolactonisation of a derivative generated the remaining two stereogenic centers. Ensuing iodide displacement was achieved using a tethering strategy, to introduce the nitrogen atom to C(5). Decarboxylative coupling of a carboxylic acid with a dialkylzinc reagent completed construction of the tridecadienyl chain.



(−)-Pseudodistomin E

The pseudodistomin alkaloid family comprises six members (Figure 1), isolated from the Okinawan tunicate

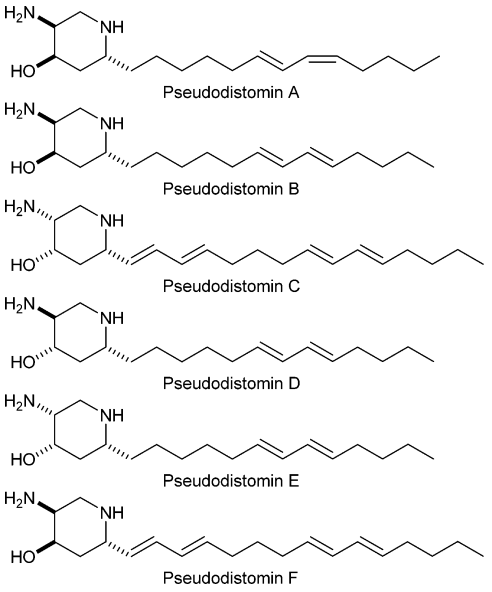


Figure 1. Structures of the pseudodistomin alkaloids.

Pseudodistoma kanoko by Kobayashi et al. in 1987 (pseudodistomins A and B)[1] and 1995 (pseudodistomin C),[2] and from the ascidian *Pseudodistoma megalarva* by Freyer et al. in 1997 (pseudodistomins D, E, and F).[3,4] Unsurprisingly, there has been interest in the development of syntheses of members of this family of alkaloids in both racemic and enantiopure form, with routes to pseudodistomins A,[5] B,[5−9] C,[10−12] D,[13,14] and F[7] having been reported to date. These endeavors have enabled not only the structures of the alkaloids to be confirmed (in fact, the structures of pseudodistomins A and B originally proposed by Kobayashi et al.[15] were revealed to be erroneous and were thus revised),[6,16,17] but also their absolute configurations. It is uniquely pseudodistomin E that remains to acquiesce to laboratory synthesis, and hence receive confirmation of its assigned structure and absolute configuration. The gross structure of pseudodistomin E was assigned by Freyer et al. using a combination of evidence, mainly gathered through NMR spectroscopic investigations.[3] ^{1}H NMR ^3J coupling constant analysis was used to assign the (*E*,*E*)-configuration to the diene unit of the side chain, as well as the relative configurations of the three stereogenic centers around the piperidine ring.[3] This analysis indicated that pseudodistomin E possessed the same relative configuration of the three stereogenic centers as pseudodistomin C. As the magnitudes of the specific rotation values of pseudodistomin E $\{[\alpha]_D^{25} - 20.8$ (*c* 0.39 in MeOH)$\}$ and pseudodistomin C $\{[\alpha]_D^{24} - 24$ (*c* 0.7 in MeOH)$\}$[18] were similar and their signs the same, and given that their structures differed only in the identity of the unsaturated hydrocarbon chain at C(2), Freyer et al. reasoned that the two natural products would be of the same enantiomeric form. As pseudodistomin C had already been shown to possess the (2*S*,4*S*,5*R*) absolute configuration by both degradation studies[2] and total synthesis from D-serine,[10] Freyer et al. assigned the (2*R*,4*S*,5*R*) absolute configuration to pseudodistomin E.[3] Herein, we report the first asymmetric synthesis of pseudodistomin E, which both confirms its structure and enables the (2*R*,4*S*,5*R*) absolute configuration of the three stereogenic centers of the piperidine ring to be assigned unambiguously.

Our asymmetric synthesis of pseudodistomin D[14] used the diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide[19] to methyl (*E*,*E*)-hepta-2,5-dienoate **1** as a stereodefining step in the preparation of lactone **7**. Elaboration of **7** to pseudodistomin D involved formal substitution of the iodide functionality by an amino functionality with overall retention of configuration.[14] We therefore envisaged elaboration of **7** to pseudodistomin E via formal substitution of

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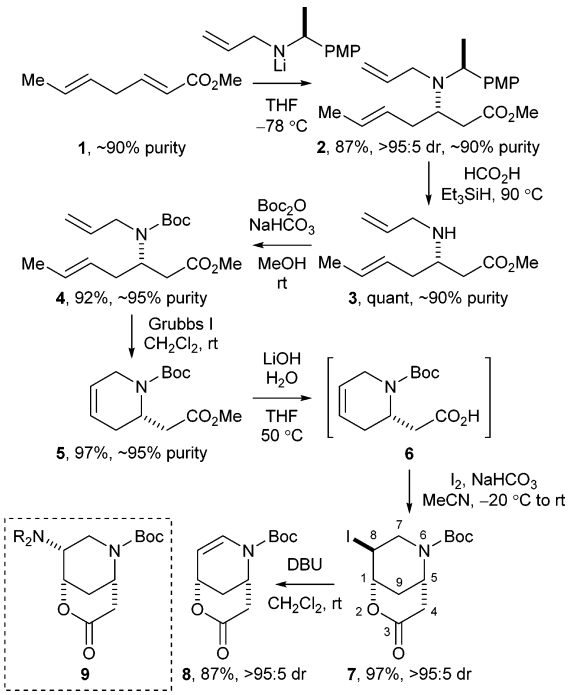
the iodide functionality by an amino functionality with overall inversion of configuration; this obviously suggested an S_N2-type reaction. Lactone **7** was prepared as previously reported,[14] in six steps and 75% overall yield from methyl (*E*,*E*)-hepta-2,5-dienoate. Attempted intermolecular displacement of the iodide functionality within **7** by a range of nucleophilic nitrogen sources (LiN_3, NaN_3, PhthNK, $BnNH_2$, Bn_2NH) was, however, thwarted by either no reaction or the formation of *N*-Boc enamine **8**, with none of the corresponding substitution product **9** being observed under any of the conditions investigated. This is consistent with an E2-type elimination dominating, which is rendered a facile process by the favorable antiperiplanar arrangement of the C(8)-iodide functionality with one of the vicinal C(7)-protons on the bicyclic framework of **7**.[20] In fact, treatment of **7** with DBU provided **8** in 87% yield (Scheme 1).

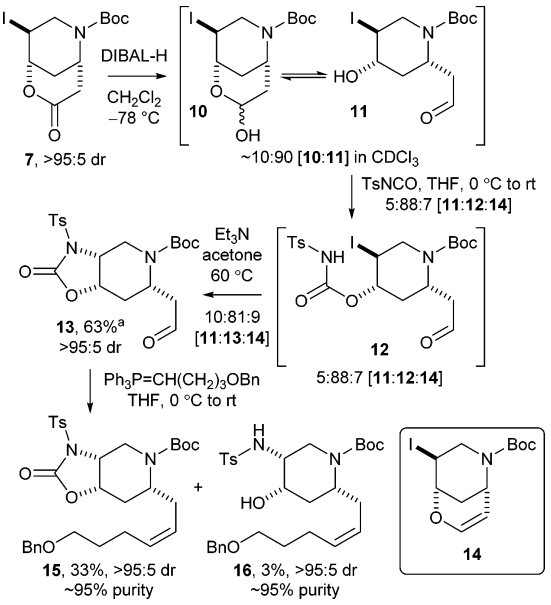
Scheme 1. Preparation of 7[a]



[a]PMP = *p*-methoxyphenyl. PhthNK = potassium phthalimide.

An alternative approach based upon tethered (i.e., intramolecular) delivery of the nucleophilic nitrogen atom was next explored.[21] Reduction of lactone **7** with DIBAL-H gave the corresponding lactol **10**, which existed mainly (~90%) as the open-chain form **11**[14] according to ^{1}H NMR spectroscopic analysis in $CDCl_3$. Treatment of **11** with TsNCO gave a 5:88:7 mixture of unreacted **11**, *N*-Ts carbamate **12**, and vinyl ether **14**, along with $TsNH_2$. Stirring this mixture with Et_3N in acetone at 60 °C resulted in formation of a 10:81:9 mixture of unreacted **11**, *N*-Ts oxazolidinone **13**, and vinyl ether **14**, along with $TsNH_2$. Purification gave **11** in 10% yield (~95% purity), **13** in 63% yield (contaminated with ~15% $TsNH_2$), and **14** in 4% yield. These product distributions suggest that a competing dehydration process is occurring: reaction of the hydroxyl functionality within the closed, lactol form **10** (rather than open-chain form **11**) with TsNCO followed by fragmentation gives **14** and *N*-tosylcarbamic acid, and decarboxylation of the latter gives $TsNH_2$.[22] Unfortunately, treatment of **13** with $Ph_3P{=}CH(CH_2)_3OBn$ [to subsequently facilitate C(2′) side-chain construction in an analogous fashion to that of our pseudodistomin D synthesis][14] delivered a complex mixture of products from which **15** was isolated in 33% yield (~95% purity) and >95:5 dr [(*Z*):(*E*) ratio]; the corresponding product **16** in which the oxazolidinone ring had been cleaved was isolated as the only other identifiable species in 3% yield (~95% purity) and >95:5 dr [(*Z*):(*E*) ratio]. The geometries of the newly formed olefins were assigned from the diagnostic values of the ^{1}H NMR ^3J coupling constants, with $^3J < 11$ Hz in both cases (Scheme 2).

Scheme 2. Attempted Preparation of 15



[a]Contaminated with ~15% $TsNH_2$.

In order to eradicate the competing dehydration pathway (and, hence, formation of $TsNH_2$), the possibility of effecting olefination of the aldehyde functionality prior to isocyanate trapping and oxazolidinone formation was considered. Although reaction of **11** with $Ph_3P{=}CH(CH_2)_3OBn$ resulted in olefination and epoxide formation (undesired in this case),[14] reaction of **11** with $Ph_3P{=}CHCO_2Me$ resulted in olefination only, with **17** being isolated in 90% yield (from **7**) and 68:32 dr [(*E*):(*Z*) ratio]. Subsequent treatment of **17** with TsNCO gave *N*-Ts carbamate **18** in 68:32 dr [(*E*):(*Z*) ratio], and then exposure of **18** to Et_3N gave *N*-Ts oxazolidinone **19** in 91% yield (from **17**) and 68:32 dr [(*E*):(*Z*) ratio]. Hydrogenation of **19** gave **20** in >95:5 dr, thus establishing conclusively that 68:32 dr corresponds to the ratio of geometric olefin isomers for **17**−**19**. Methanolysis of the carbamate functionality within **20** using K_2CO_3 in MeOH gave **21** in 77% yield (from **19**). The relative configuration of **21** was then assigned from ^{1}H NMR ^3J coupling constant analysis, assuming a chair conformation. This not only established the relative configurations within **19** and **20** but also that the formal substitution of the iodide functionality by an amino functionality had proceeded with inversion of configuration, as required for the synthesis of pseudodistomin E. With this transformation (i.e., **7** to **19**) established, an end-game for the elaboration of lactone **7** into pseudodistomin E using the decarboxylative coupling of a carboxylic acid and a dialkylzinc reagent, recently reported by Baran et al.,[23] was envisaged. Thus, sequential treatment of lactone **7** with DIBAL-H, $Ph_3P{=}CHCO_2Bn$, TsNCO and Et_3N gave *N*-Ts oxazolidinone **24** (the

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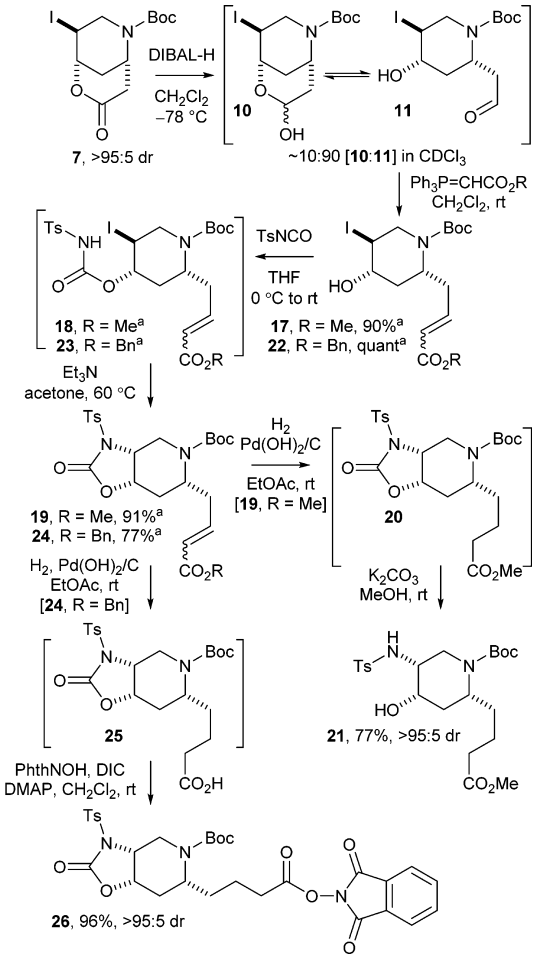
analogue of **19** with a pendant benzyl rather than methyl ester) in 77% overall yield and 68:32 dr [(*E*):(*Z*) ratio]. Tandem hydrogenation/hydrogenolysis of **24** gave carboxylic acid **25** which was coupled with PhthNOH to give activated ester **26** in 96% yield and >95:5 dr (Scheme 3). The coupling partner, (*E*,*E*)-

Scheme 3. Preparation of 26

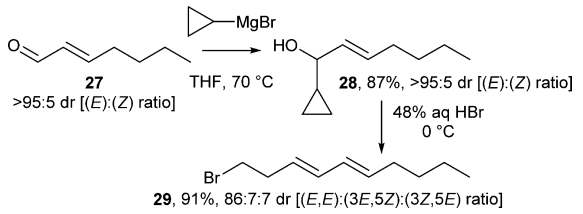


[a]68.32 dr [(*E*):(*Z*) ratio]. PhthNOH = *N*-hydroxyphthalimide. DIC = *N*,*N*′-diisopropylcarbodiimide.

1-bromodeca-3,5-diene **29**, was prepared via 1,2-addition of cyclopropylmagnesium bromide to (*E*)-2-heptenal **27** (>95:5 dr) and then rearrangement/substitution of the resultant secondary alcohol **28** promoted by 48% aq HBr for 24 h[24] which gave **29** in 86:7:7 dr [(*E*,*E*):(3*E*,5*Z*):(3*Z*,5*E*) ratio] and 91% isolated yield (Scheme 4).

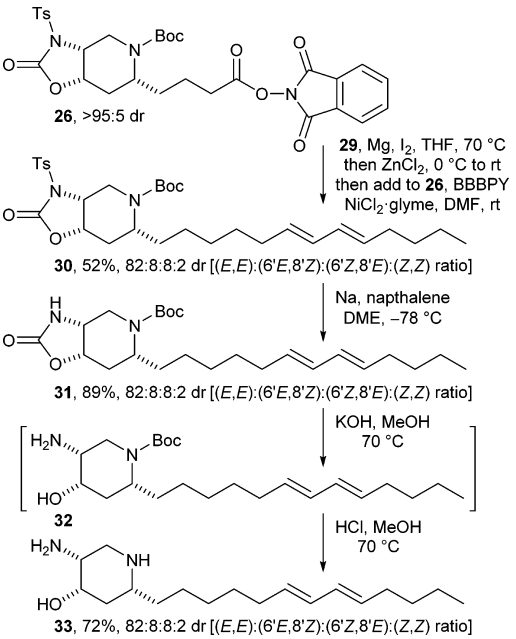
Following Baran's protocol,[23] ester **26** was coupled with bromide **29** to give **30** in 52% yield and 82:8:8:2 dr [(*E*,*E*):(6′*E*,8′*Z*):(6′*Z*,8′*E*):(*Z*,*Z*) ratio]. The final stages involved *N*-

Scheme 4. Preparation of 29



and *O*-deprotection: the *N*-Ts group was removed from **30** upon treatment with sodium naphthalenide to give **31** in 89% yield and 82:8:8:2 dr [(*E*,*E*):(6′*E*,8′*Z*):(6′*Z*,8′*E*):(*Z*,*Z*) ratio], the oxazolidinone moiety within **31** was cleaved using KOH in hot MeOH to give **32**, and finally the *N*-Boc group was removed from **32** using HCl in hot MeOH to give synthetic pseudodistomin E **33** in 72% yield (from **31**) and 82:8:8:2 dr [(*E*,*E*):(6′*E*,8′*Z*):(6′*Z*,8′*E*):(*Z*,*Z*) ratio] after purification basification and by chromatography; further separation of these olefin isomers was not attempted. As the lithium amide reagent used for the conjugate addition reaction was >99% ee, **33** was inferred as being >99% ee, along with all intermediates en route (Scheme 5).

Scheme 5. Preparation of Synthetic Pseudodistomin E 33[a]



[a]BBBPY = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

^{1}H NMR ^3J coupling constant analysis of **33** was evincive of the relative configuration around the piperidine ring [a chair conformation with the C(2)- and C(4)-substituents equatorial, and the C(5)-substituent axial], as well as the (*E*,*E*)-geometry of the diene unit.[25] As may be reasonably expected for a compound containing two basic amino functionalities, the ^{1}H and ^{13}C NMR spectroscopic data of **33** showed significant variance upon introduction of trifluoroacetic acid (in 0.1 equiv portions) to the sample (Figure 2 and Supporting Information). A similar effect on the magnitude of the specific rotation value of **33** was also noted: for example we obtained $[\alpha]_D^{25}$ − 34.5 (*c* 1.0 in MeOH) and $[\alpha]_D^{25}$ − 9.2 (*c* 1.0 in 1.25 M methanolic HCl). Comparison of our spectroscopic and physical data for **33** with those reported by Freyer et al. for pseudodistomin E[3] revealed excellent agreement of the ^{1}H NMR spectroscopic data of **33** (free base) with those of the natural product ($\Delta\delta_H \leq 0.02$ ppm).[26] Meanwhile, the ^{13}C NMR spectroscopic data of **33**·0.1TFA showed excellent parity with those reported for the natural product ($\Delta\delta_C \leq 0.2$ ppm),[26] suggesting that traces of acid were present in the sample of the natural product when the ^{13}C NMR spectrum was recorded. The specific rotation of **33**·0.1TFA was measured as $[\alpha]_D^{25}$ − 22.0 (*c* 0.5 in MeOH), which compares favorably with $[\alpha]_D^{25}$ − 20.8 (*c* 0.39 in MeOH)} reported by Freyer et al. for pseudodistomin E.[3] It can thus be concluded that

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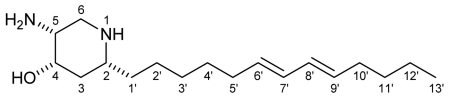

proton #	pseudodistomin E	33
2	2.44 (m)	2.46 (m)
3-A	1.21 (ddd, *J* 12.7, 11.7, 11.4)	1.22 (app q, *J* 11.8)
3-B	1.68 (dddd, *J* 12.7, 4.0, 2.7, 0.8)	1.68 (ddd, *J* 12.8, 4.3, 2.7)
4	3.67 (ddd, *J* 11.7, 4.8, 4.0)	3.67 (app dt, 11.5, 4.4)
5	2.90 (m)	2.90 (m)
6-A	2.73 (dd, *J* 13.3, 2.5)	2.73 (dd, *J* 13.3, 2.5)
6-B	2.98 (dd, *J* 13.3, 2.5)	2.98 (dd, *J* 13.3, 2.5)
1'-4', 11', 12'	1.35 (m)	1.36 (m)
5', 10'	2.05 (dt, *J* 7.1, 7.0)	2.06 (m)
6', 9'	5.52 (m)	5.53 (m)
7', 8'	5.96 (m)	5.98 (m)
13'	0.90 (t, *J* 7.1)	0.91 (t, *J* 7.1)

carbon #	pseudodistomin E	33	33·0.1TFA
2	56.4	56.5 (0.1)	56.5 (0.1)
3	35.3	35.6 (0.3)	35.2 (0.1)
4	69.7	71.0 (1.3)	69.6 (0.1)
5	51.3	51.4 (0.1)	51.3 (0.1)
6	49.3	50.4 (1.1)	49.3 (0.0)
1'	36.9	37.4 (0.5)	36.8 (0.1)
2'	26.6	26.9 (0.3)	26.7 (0.1)
3'	30.2	30.5 (0.3)	30.4 (0.2)
4'	30.4	30.6 (0.2)	30.6 (0.2)
5'	33.3	33.5 (0.2)	33.4 (0.1)
6'	132.8	133.0 (0.2)	133.0 (0.2)
7'	132.0	132.1 (0.1)	132.1 (0.1)
8'	131.8	132.0 (0.2)	132.0 (0.2)
9'	133.1	133.2 (0.1)	133.2 (0.1)
10'	33.5	33.7 (0.2)	33.6 (0.1)
11'	32.8	33.0 (0.2)	33.0 (0.2)
12'	23.3	23.4 (0.1)	23.4 (0.1)
13'	14.3	14.5 (0.2)	14.4 (0.1)

Figure 2. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectroscopic data for pseudodistomin E and synthetic **33** in d_4-MeOH. Values of $\Delta\delta_C$ are given in parentheses.

33 and pseudodistomin E are identical, hence establishing unambiguously the structure and (2*R*,4*S*,5*R*) absolute configuration of the natural product.

In conclusion, the first asymmetric synthesis of (−)-pseudodistomin E has been achieved in 16 steps from methyl (*E*,*E*)-hepta-2,5-dienoate, and in 19% overall yield and >99% ee. Conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to methyl (*E*,*E*)-hepta-2,5-dienoate generated the C(2)-stereocenter of the target, with regioselective iodolactonisation of a derivative being used to construct the remaining C(4)- and C(5)-stereocenters. Iodide displacement (with inversion of configuration) was achieved using a tethering strategy, and set the absolute C(5)-stereochemistry required for the target. The unsaturated C(2)-hydrocarbon chain was constructed using a decarboxylative coupling of a carboxylic acid with a dialkylzinc reagent. Comparison of NMR spectroscopic and specific rotation data of our synthetic sample with those of the natural product established conclusively both the structure and (2*R*,4*S*,5*R*) absolute configuration of pseudodistomin E.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00434.

Experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Pseudodistomin A was originally assigned as (2*R*,4*R*,5*S*,3′*E*,5′*Z*)-2-(trideca-3′,5′-dien-1′-yl)-5-aminopiperidin-4-ol and pseudodistomin B was originally assigned as (2*R*,4*R*,5*S*,*E*,*E*)-2-(trideca-3′,5′-dien-1′-yl)-5-aminopiperidin-4-ol (see ref 1).

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(18) No specific rotation value for pseudodistomin C was reported in either of the two publications detailing its isolation (see ref 2 and ref 3); the value quoted is for the synthetic sample prepared by Kobayashi et al. (see ref 10).

(19) For development of lithium *N*-allyl-*N*-(α-methylbenzyl)amide, see: Davies, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387.

(20) The solid state conformation of **7** (see ref 14) displays this geometric arrangement.

(21) For examples of this tactic, see: (a) Knapp, S.; Kukkola, P. J.; Sharma, S.; Pietranico, S. *Tetrahedron Lett.* **1987**, *28*, 5399. (b) Das, J. *Synth. Commun.* **1988**, *18*, 907.

(22) The ratio of vinyl ether **14** to $TsNH_2$ was ∼ 1:1 in the ^{1}H NMR spectrum of both of the relevant crude reaction mixtures.

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(25) $^{3}J_{6',7'}$ and $^{3}J_{8',9'}$ were discerned as > 15 Hz.

(26) $\Delta\delta_X = |\delta_X$ (synthetic) − δ_X (natural)|, where X = H or C.

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