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Polysubstituted Piperidines via Iodolactonization: Application to the Asymmetric Synthesis of (+)-Pseudodistomin D

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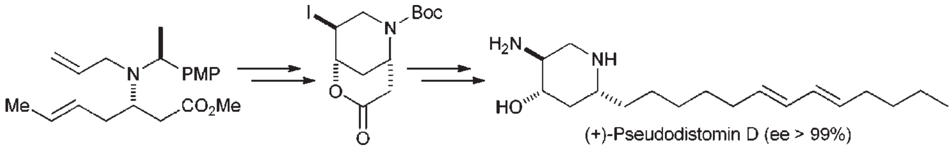
ABSTRACT



Conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to methyl (*E*,*E*)-hepta-2,5-dienoate furnished the corresponding β-amino ester. *N*-Protecting group manipulation, ring-closing metathesis, and ester hydrolysis gave enantiopure [*N*(1′)-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridin-2′-yl]ethanoic acid. Subsequent iodolactonization gave a bicyclic iodolactone scaffold. This key intermediate was elaborated to (+)-pseudodistomin D [in >99% ee and 7% yield over 16 steps from methyl (*E*,*E*)-hepta-2,5-dienoate].

The pseudodistomin alkaloids were the first piperidine alkaloids to be isolated from a marine source, namely the Okinawan tunicate *Pseudodistoma kanoko*[1] and (later) the ascidian *Pseudodistoma megalarva*.[2] Six members of the family (pseudodistomins A–F) have so far been isolated, the structures of which differ in either the relative stereochemistry of the C(2)-alkyl chain, C(4)-hydroxyl, and C(5)-amino substituents of the piperidine ring, or in the structure of the C(2)-alkyl chain (Figure 1).[3] Pseudodistomin E is yet to acquiesce to laboratory synthesis, while routes to pseudodistomins A,[3f,4] B,[3b,4,5] C,[6] D,[7] and F[5a] have been reported.[8,9]

We have previously demonstrated that the ring-closing metathesis of enantiopure, substituted *N*-allyl-*N*-but-3-

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[1] (a) Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem.* **1987**, *52*, 450. (b) Kobayashi, J.; Cheng, J. F.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Walchli, M. R.; Sasaki, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1988**, *30*, 268. (c) Kobayashi, J.; Naitoh, K.; Doi, Y.; Deki, K.; Ishibashi, M. *J. Org. Chem.* **1995**, *60*, 6941.

[2] Freyer, A. J.; Patil, A. D.; Killmer, L.; Troupe, N.; Mentzer, M.; Carte, B.; Faucette, L.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 986.

[3] The initially proposed structures of pseudodistomins A and B (see ref 1a and ref 1b) were subsequently revised (to those shown in Figure 1) following synthetic studies and degradation experiments performed on the natural products; see: (a) Naito, T.; Yuumoto, Y.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1992**, *33*, 4033. (b) Kiguchi, T.; Yuumoto, Y.; Ninomiya, I.; Naito, T.; Deki, K.; Ishibashi, M.; Kobayashi, J. *Tetrahedron Lett.* **1992**, *33*, 7389. (c) Kiguchi, T.; Yuumoto, Y.; Ninomiya, I.; Naito, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1992**, *34*, 392. (d) Ishibashi, M.; Deki, K.; Kobayashi, J. *J. Nat. Prod.* **1995**, *58*, 804. (e) Naito, T.; Yuumoto, Y.; Kiguchi, T.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, *3*, 281. (f) Kiguchi, T.; Yuumoto, Y.; Ninomiya, I.; Naito, T. *Heterocycles* **1996**, *42*, 509.

[4] Kiguchi, T.; Yuumoto, Y.; Ninomiya, I.; Naito, T. *Chem. Pharm. Bull.* **1997**, *45*, 1212.

[5] (a) Ma, D.; Sun, H. *J. Org. Chem.* **2000**, *65*, 6009. (b) Davis, F. A.; Zhang, J.; Li, Y.; Xu, H.; DeBrosse, C. *J. Org. Chem.* **2005**, *70*, 5413.

[6] Doi, Y.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573. Langlois, N. *Org. Lett.* **2002**, *4*, 185. Tanaka, K.; Maesoba, T.; Sawanishi, H. *Heterocycles* **2006**, *68*, 183.

[7] Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823.

[8] Several total syntheses (both racemic and asymmetric) of tetrahydropseudodistomin (the product resulting from hydrogenation of either pseudodistomin A or pseudodistomin B) have also been reported; see: ref 3a, ref3e and (a) Utsunomiya, I.; Ogawa, M.; Natsume, M. *Heterocycles* **1992**, *33*, 349. (b) Knapp, S.; Hale, J. J. *J. Org. Chem.* **1993**, *58*, 2650. (c) Kiguchi, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 893. For a synthesis of octahydropseudodistomin F, see: (d) Ma, D.; Sun, H. *Tetrahedron Lett.* **1999**, *40*, 3609. For syntheses of the funcationalized piperidine core, see: (e) Kiguchi, T.; Okazaki, M.; Naito, T. *Heterocycles* **1999**, *51*, 2711. (f) Haddad, M.; Larcheveque, M.; Tong, H. M. *Tetrahedron Lett.* **2005**, *46*, 6015. (g) Leonard, N. M.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 6915.

[9] For reviews (including discussion of the structural revision of pseudodistomins A and B), see: (a) Kobayashi, J.; Ishibashi, M. *Heterocycles* **1996**, *42*, 943. (b) Ninomiya, I.; Kiguchi, T.; Naito, T. *The Alkaloids* **1998**, *50*, 317. (c) Kobayashi, J.; Ishibashi, M. *Stud. Nat. Prod. Chem.* **2000**, *23*, 185.

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enyl amines (prepared via our lithium amide conjugate addition methodology)[10] represents a rapid and efficient entry to substituted tetrahydropyridine scaffolds, and have demonstrated the elaboration of these useful templates to a range of Sedum alkaloids,[11] the Hemlock alkaloid coniine,[12] and homopipecolic acid **4**[12] (Scheme 1). In order to further extend this useful methodology, we envisaged that iodolactonization of an enantiopure tetrahydropyridine scaffold (such as the carboxylic acid resulting from ester hydrolysis of **3**) would generate the corresponding iodolactone with high diastereoselectivity and that this template would act as a key intermediate for the synthesis of a range of alkaloid natural products, including the pseudodistomin alkaloids and their analogues. We delineate herein our preliminary investigations in this area, which culminate in the synthesis of pseudodistomin D. To date, only one other asymmetric synthesis of this natural product has been reported by Trost and Fandrick.[7] Their approach employed dynamic kinetic resolution (DKR) of a vinyl aziridine, epoxidation of an allylic carbamate with *m*-CPBA, and a reductive alkyne hydroamination step to set the stereochemistry within the piperidine core of the final product, and delivered pseudodistomin D in 12% yield and 94% ee over 12 steps from ethyl 2,4-dibromopropionate.

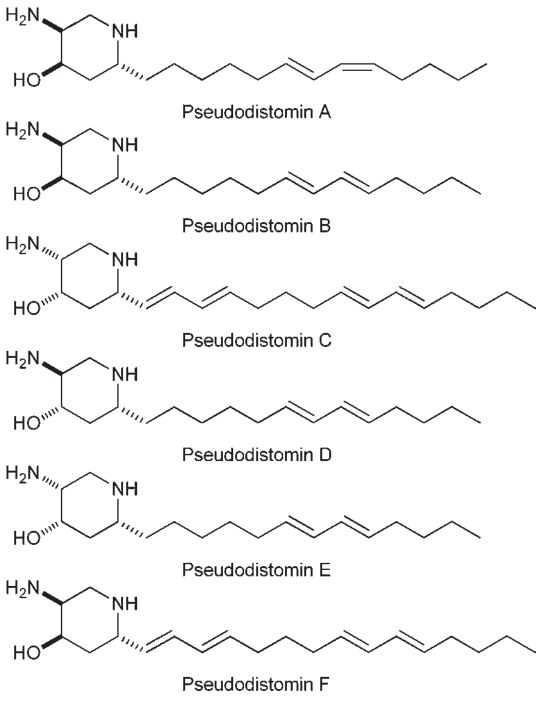
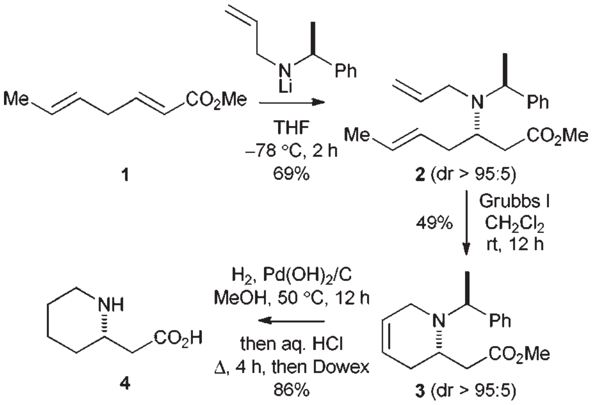


Figure 1. Structures of the pseudodistomin alkaloids.

Scheme 1



Saponification of **3**[12] gave the corresponding carboxylic acid, but attempts at effecting iodolactonization of this substrate returned only complex mixtures of products, possibly due to competing oxidative processes at the nitrogen atom. In order to suppress any such unwanted side reactions, an alternative strategy was devised. Conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide (>99% ee)[13] to methyl (*E*,*E*)-hepta-2,5-dienoate **1**[14] gave *β*-amino ester (*S*,*S*)-**5** in >95:5 dr, which was isolated in 59% yield (~90% purity). The absolute (*S*,*S*)-configuration within **5** was assigned by reference to the transition state mnemonic developed by us to rationalize the very high facial selectivity observed upon conjugate addition of this class of lithium amides to α,*β*-unsaturated esters and amides.[15] Chemoselective removal of the *N*-α-methyl-*p*-methoxybenzyl group within **5** was achieved upon treatment with formic acid in the presence of triethylsilane,[16] with subsequent *N*-Boc protection of the resultant secondary amine **6** giving *tert*-butyl carbamate **7**[17] in 80% yield over the 2 steps. Treatment of **7** with Grubbs I gave tetrahydropyridine **8** in 97% isolated yield, with saponification of **8** giving carboxylic acid **9** quantitatively (Scheme 2).

Iodolactonization of **9** upon treatment with I_2 and $NaHCO_3$ in MeCN proceeded to give the bicyclic iodolactone **10** in 87% isolated yield as a single diastereoisomer (Scheme 3). The relative configuration within **10** was

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(10) (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183. (b) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833. (c) Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Price Mortimer, A. J.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793. (d) Davies, S. G.; Mulvaney, A. W.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1554. (e) Davies, S. G.; Fletcher, A. M.; Roberts, P. M. *Org. Synth.* **2010**, *87*, 143.

(11) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.

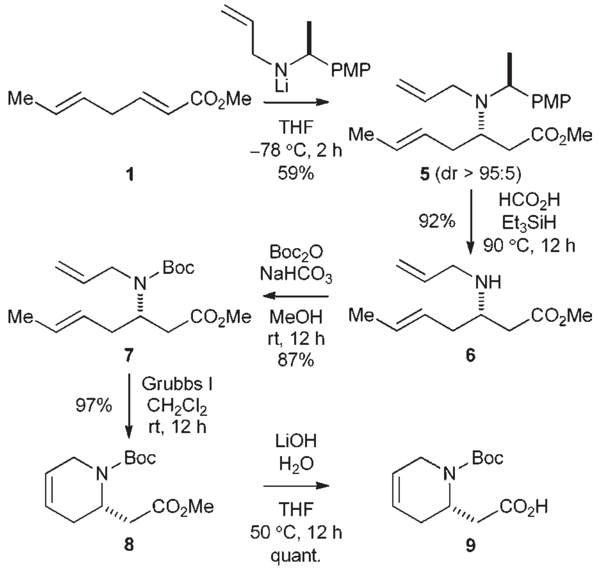
(12) (a) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146. (b) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.

(13) Enantiopure (*S*)-α-methyl-*p*-methoxybenzylamine (>99% ee) is commercially available. Alkylation of (*S*)-α-methyl-*p*-methoxybenzylamine upon treatment with BuLi followed by allyl bromide gave (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amine; subsequent deprotonation with BuLi in THF generated a yellow solution of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide.

(14) Methyl (*E*,*E*)-hepta-2,5-dienoate **5** was prepared via palladium-catalyzed coupling of methyl acrylate with 1,3-butadiene according to our previously reported procedure; see: Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Price Mortimer, A. J.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630.

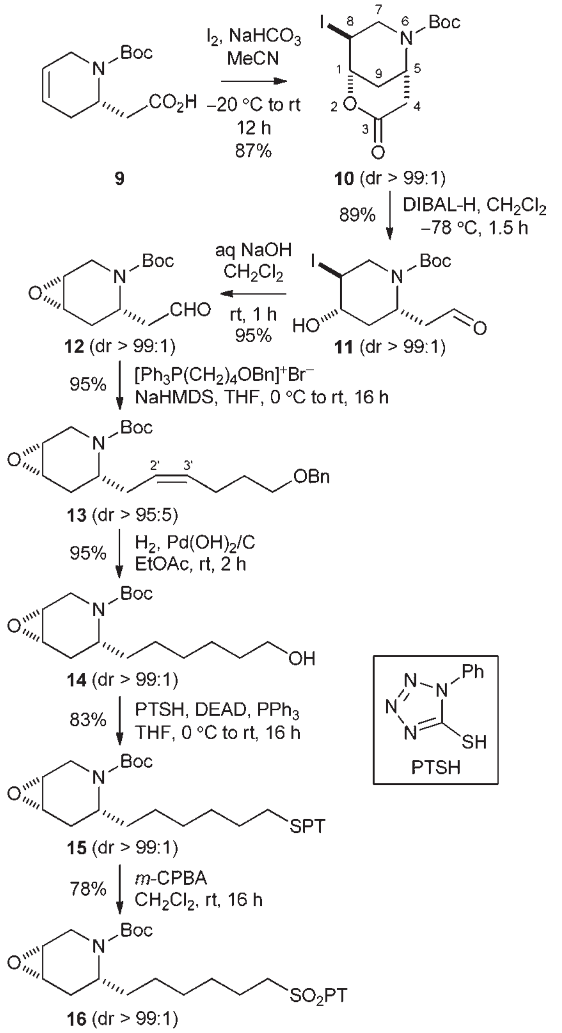
(15) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

Scheme 2[a]



[a] PMP = *p*-methoxyphenyl.

Scheme 3



unambiguously established by single-crystal X-ray diffraction analysis (Figure 2),[18] with the absolute (*S*,*S*,*S*)-configuration being assigned by inference from the configuration of the C(5)-stereocenter, originally formed upon conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to α,*β*-unsaturated ester **1**.[15] Reduction of lactone **10** with DIBAL-H followed by treatment of the resultant iodohydrin **11** with aq. NaOH gave aldehyde **12** in 85% yield over the 2 steps. Wittig olefination of **12** with the ylide derived from $[Ph_3P(CH_2)_4OBn]^+Br^-$[19] gave alkene **13** in 95% yield. Due to overlapping resonances in the ^{1}H NMR spectrum of both the crude and purified product, the diastereoselectivity of this olefination reaction was tentatively assessed as >95:5. The (*Z*)-configuration was assigned to the major diastereoisomeric product **13** on the basis of ^{1}H NMR ^3J coupling constant analysis ($J_{2',3'} < 11$ Hz), and by analogy to the well-established stereochemical outcome of this type of Wittig olefination reaction.[20] In any case, subsequent treatment of **13** with H$_2$ in the presence of Pd(OH$_2$)/C gave alcohol **14** in 95% isolated yield as a single diastereoisomer. Mitsunobu reaction[21] of **14** with *N*(1)-phenyl-1*H*-tetrazole-5-thiol (PTSH) gave sulfide **15** in 83% yield, and subsequent oxidation upon treatment of **15** with *m*-CPBA gave sulfone **16** in 78% isolated yield (Scheme 3).

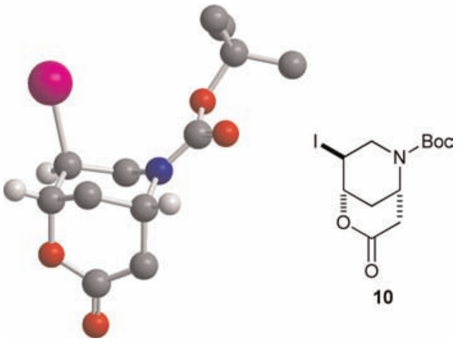


Figure 2. Chem 3D representation of the single crystal X-ray diffraction structure of **10** (selected H-atoms are omitted for clarity).

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(16) Zhong, M. H.; Cohen, J. H.; Abdel-Magid, A. F.; Kenney, B. D.; Maryanoff, C. A.; Shah, R. D.; Villani, F. J., Jr.; Zhang, F.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 7721.

(17) *tert*-Butyl carbamate **7** and all subsequent carbamate-containing compounds in this synthesis were rotameric in CDCl$_3$ (and PhMe-d_8 or DMSO-d_6) at rt. However, coalescence occurred when the spectrum was recorded at 90 °C (in PhMe-d_8 or DMSO-d_6).

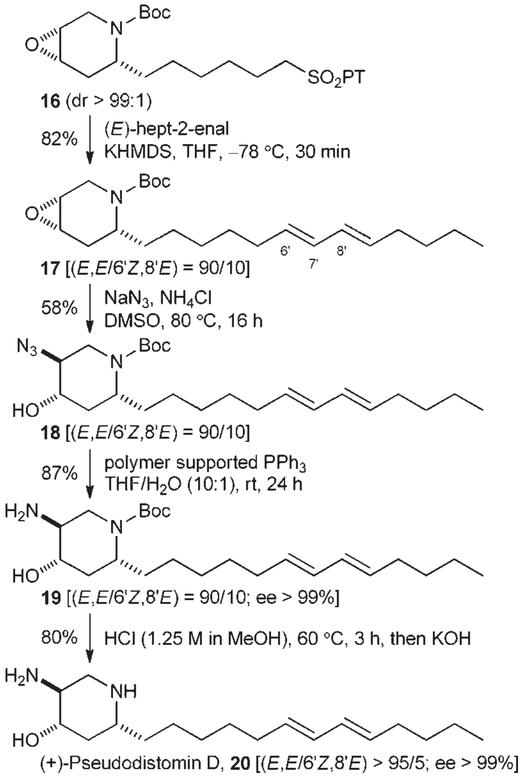
(18) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 858971.

(19) $[Ph_3P(CH_2)_4OBn]^+Br^-$ was prepared from butane-1,4-diol (92% yield over 3 steps).

(20) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(21) (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935. (b) Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (c) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551.

Scheme 4



Julia–Kocieński olefination[22] of sulfone **16** with (*E*)-hept-2-enal (commercially available, 97% purity) furnished (*E*,*E*)-**17** in 90:10 dr, which was isolated in 82% yield (and 90:10 dr) after chromatography [the minor product was assigned as the (6′*Z*,8′*E*)-isomer].[23] Ring opening of the epoxide functionality within **17** upon treatment with NaN$_3$ in the presence of NH$_4$Cl in DMSO gave an ~75:25 mixture of regioisomeric azides **18** and **18′**, from which the major product **18** was isolated in 58% yield and 90:10 dr [(*E*,*E*)/(6′*Z*,8′*E*)] and the minor product **18′** in 20% yield and 90:10 dr [(*E*,*E*)/(6′*Z*,8′*E*)]. Reduction of **18** under Staudinger conditions[24] gave aminopiperidine **19**, which was isolated in 87% yield, 90:10 dr [(*E*,*E*)/(6′*Z*,8′*E*)], and > 99% ee.[25] Finally, treatment of **19** with HCl in MeOH gave pseudodistomin D as its hydrochloride salt, with subsequent sequential recrystallization and basification giving pseudodistomin D **20** in 80% yield and > 95:5 dr [(*E*,*E*)/(6′*Z*,8′*E*)]. The spectroscopic properties of our synthetic sample of pseudodistomin D **20** were in excellent agreement with those originally reported for the natural product {$[\alpha]_D^{25}$ +5.6 (*c* 0.3 in MeOH); lit.[2] for sample isolated from natural source $[\alpha]_D^{25}$ +5 (*c* 0.26 in MeOH)} and with the synthetic sample reported by Trost and Fandrick {lit.[7] $[\alpha]_D^{25}$ +6 (*c* 0.2 in MeOH) for 94% ee}. Given the known enantiomeric purity of the lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **12** (i.e., > 99% ee) employed for the conjugate addition to α,*β*-unsaturated ester **1**, and the enantiomeric purity of aminopiperidine **19** (i.e., > 99% ee), the enantiomeric purity of pseudodistomin D **20** and intermediates **5**–**18** (and **18′**) can be confidently inferred as > 99% ee (Scheme 4).

In conclusion, conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to methyl (*E*,*E*)-hepta-2,5-dienoate furnished the corresponding *β*-amino ester. *N*-Protecting group manipulation, ring-closing metathesis, and ester hydrolysis gave enantiopure [*N*(1′)-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridin-2′-yl]ethanoic acid. Subsequent iodolactonization gave a bicyclic iodolactone scaffold. This key intermediate was elaborated to (+)-pseudodistomin D [in > 99% ee and 7% yield over 16 steps from methyl (*E*,*E*)-hepta-2,5-dienoate]. The key bicyclic iodolactone intermediate of this synthesis should prove readily applicable to diversification to facilitate the synthesis of the other members of the pseudodistomin family, and further investigations toward this aim are currently underway within our laboratory.

Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information file (for structure CCDC 858971). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26.

(23) This assignment was made from the known purity of the (*E*)-hept-2-enal used in the olefination reaction, and from comparison of the ^{13}C NMR chemical shift values associated with the diene moiety in the alkyl side chain of the minor diastereoisomeric product with those previously reported for pseudodistomin A triacetate [i.e., (6′*E*,8′*Z*)] and its (6′*Z*,8′*E*)-geometric isomer; see: ref 3f.

(24) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) Gololobov, Y. G. *Tetrahedron* **1981**, *37*, 437.

(25) The enantiomeric purity of **20** was confirmed as > 99% ee by 500 MHz ^{1}H NMR spectroscopic analyses in the presence of (*S*)-*O*-acetylmandelic acid and (*R*,*S*)-*O*-acetylmandelic acid; see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441. This value is consistent with the enantiomeric purity of the lithium (*S*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **12** (i.e., > 99% ee) employed for the conjugate addition to α,*β*-unsaturated ester **1**.

The authors declare no competing financial interest.