Synthesis of (+)-Tetrahydropseudodistomin

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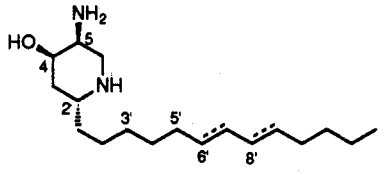
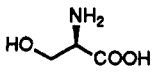
Summary: The stereocontrolled synthesis of (+)-tetrahydropseudodistomin (**3**) from D-serine features the use of the dibenzyltriazone group for amino protection and establishes the absolute stereochemistry of the naturally occurring calmodulin antagonists pseudodistomin A and B (**1** and **2b**, respectively).

Pseudodistomins A and B are isomeric piperidine alkaloids that were isolated from the Okinawan tunicate *Pseudodistoma kanoko* and shown to possess in vitro antitumor activity against L1210 and L5178 leukemia cells and to inhibit calmodulin-activated brain phosphodiesterase.[1] They were initially assigned structures **1** and **2a**, respectively, based on ^1H and ^{13}C NMR, UV, MS, and



1 (pseudodistomin A): 3'-*trans*, 5'-*cis* -diene (?)
2a (pseudodistomin B, initial): 3'-*trans*, 5'-*trans*
2b (pseudodistomin B, revised): 6'-*trans*, 8'-*trans*
3 (tetrahydro-pseudodistomin): 6', 8'-*saturated*

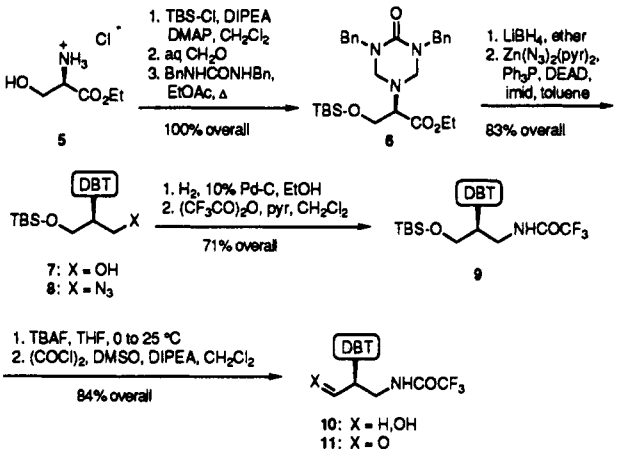


4 (D-serine)

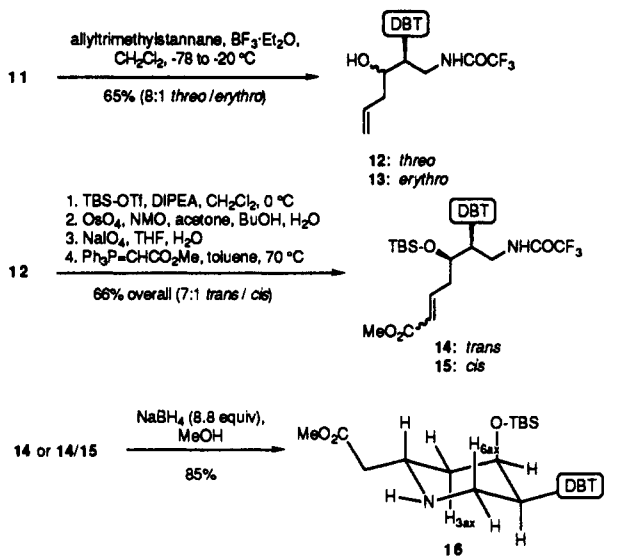
exciton coupling analysis of the natural products, the saturated derivative **3**, and their acylated derivatives.[1] A recent synthesis[2] of the triacetate of racemic **2a** questioned the assignment of the side-chain diene portion as first presented,[1] and further degradation studies of pseudodistomin B and synthesis of the racemic triacetate led to the revised assignment as the 6',8'-diene **2b**.[3] We have no developed a synthesis of (+)-tetrahydropseudodistomin **3** from D-serine that confirms the piperidine ring absolute stereochemistry of **1** and **2b** as 2(*R*),4(*R*),5(*S*).[4]

D-Serine (**4**) possesses a three-carbon chain with functionality and absolute stereochemistry that are appropriate for elaboration to C-4,5,6 of the pseudodistomins. Furthermore, we have recently converted the amino group of several α-amino acid derivatives to the dibenzyltriazone, a nonpolar protection group that withstands a variety of functional group transformations and C–C bond forming reactions and also slows racemization of the derived α-amino aldehydes.[5] Thus ethyl D-serinate hydrochloride **5** (Scheme I) was O-silylated and converted to its dibenzyltriazone derivative **6**. Reduction of the ester followed by Mitsunobu reaction[6] with $Zn(N_3)_2$ gave the azide **8**.

Scheme I



Scheme II



The azido group was reduced and protected as its *N*-trifluoroacetate **9**. O-Desilylation and then Swern oxidation of the alcohol **10** led to the protected 2,3-diaminopropanal **11**. That no racemization of intermediates had occurred was demonstrated by reduction of **11** back to **10**; the (*S*)-Mosher ester[5] of **10** (whether from **9** or **11**) had de >98.

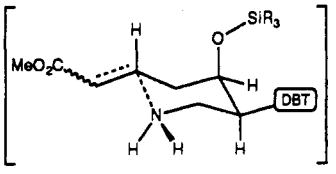
Lewis acid-promoted addition[7] of allyltrimethylstannane to aldehyde **11** (Scheme II) occurred with 8:1 Cram's-rule stereoselectivity to afford the homoallylic alcohols **12** and **13**; pure **12** was obtained after crystallization. The stereochemistry of **12** and **13**, later confirmed, was initially assigned based on precedent for this addition[7] and on ^1H NMR spectroscopic comparison using closely related α-amino aldehyde adducts of proven structure as models.[8] After hydroxyl protection, the carbon chain was extended by oxidative cleavage of the alkene and then Wittig reaction

(1) Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem.* **1987**, *52*, 450.
(2) Naito, T.; Yuumoto, Y.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1992**, *33*, 4033. This paper also describes the synthesis of the triacetate of racemic **3**.
(3) Kiguchi, T.; Yuumoto, Y.; Ninomiya, I.; Naito, T.; Deki, K.; Ishibashi, M.; Kobayashi, J. *Tetrahedron Lett.* **1992**, *33*, 7389. As the result of this work, structure **1** proposed for pseudodistomin A must also be questioned.
(4) A synthesis of **3** as appeared: Utsunomiya, I.; Ogawa, M.; Natsume, M. *Heterocycles* **1992**, *33*, 349.
(5) Knapp, S.; Hale, J. J.; Bastos, M.; Molina, A.; Chen, K. Y. *J. Org. Chem.* **1992**, *57*, 6239.
(6) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.
(7) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.

0022-3263/93/1958-2650$04.00/0

of the resulting aldehyde to afford the unsaturated esters **14** and **15** as a readily separable 7:1 trans/cis mixture. Methanolic sodium borohydride[9] removed the *N*-trifluoroacetate from either pure **14** or the mixture and triggered an intramolecular Michael reaction in which piperidine **16** formed as the only cyclized product in either case. The stereochemistry of **16** follows unambiguously from the ^1H–^1H coupling constants. In particular, both H_{3ax} and H_{6ax} appear as triplets (J = 12 and 10.5, respectively) as the result of similar couplings with geminal equatorial and vicinal trans-axial neighbors. Methanolic sodium methoxide also converted **14** to **16** stereoselectively, but the yield was only 25%.

The indication that piperidine **16** exists in a chair form with the bulky dibenzyltriazone group and the two-carbon chain occupying equatorial positions (and the protected hydroxyl an axial position) helps to rationalize the high kinetic stereoselectivity in the cyclization reaction. Comparison of two folded chairlike transition states (**17** and **18**) leading to **16** and its C_2-epimer, respectively, reveals a potential steric repulsion involving the (*tert*-butyldimethylsilyl)oxy group and the vinyl proton (or methoxycarbonyl group in the case of the cis isomer **15**) for **18** that has no counterpart in **17**.



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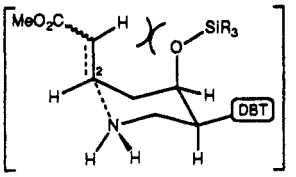

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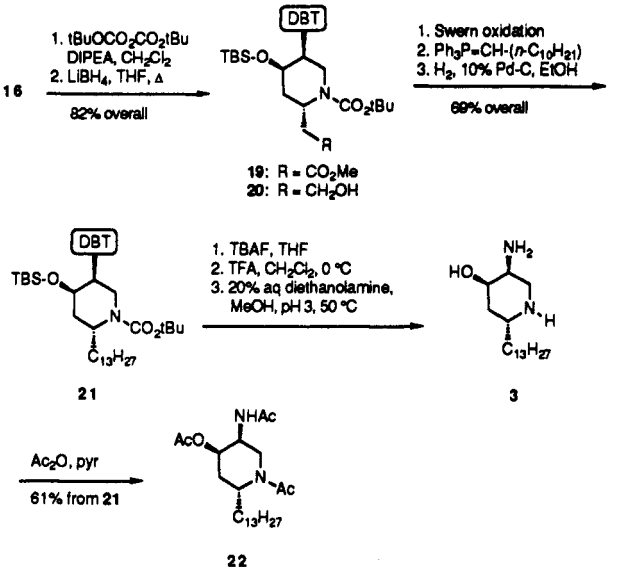
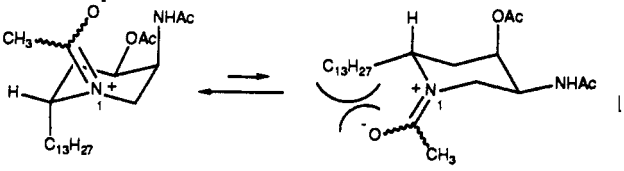
Completion of the synthesis of **3** and its *N,N',O*-triacetate **22** is shown in Scheme III. N-1 of **16** was protected as the *tert*-butoxycarbonyl derivative, and the ester was reduced to give the primary alcohol **20**. The remainder of the side chain was attached by means of Swern oxidation, Wittig reaction with undecylidenetriphenylphosphorane, and then hydrogenation to give the protected tetrahydropseudodistomin **21**. Sequential deprotection was carried out by using tetra-*n*-butylammonium floride to remove *O*-(*tert*-butyldimethylsilyl), trifluoroacetic acid to remove *N*-*tert*-butoxycarbonyl, and then aqueous diethanolamine at pH 3 to cleave the dibenzyltriazone group[5] and afford the crude diamino alcohol **3**. Acetylation gave the triacetate **22** ($[\alpha]_D$ = +36.9°, c = 0.8, MeOH (lit.[1] $[\alpha]_D$ = +33°, c = 1, MeOH)), whose structure was confirmed by ^1H and ^{13}C NMR spectroscopic analysis, and by HRMS. Two amide rotamers, with a 2:1 ratio and nearly identical ^1H–^1H J values, are apparent from the ^1H NMR spectrum, as has been reported for the triacetates of **1** and **2**.[1] The signals for the major rotamer match

Scheme III



closely those reported[1] for **22**. ^1H NMR analysis[1] also indicates an axial acetamido group for **22** in deuteriochloroform solution (see **22-A**), which can be understood by observing that the alternative chair conformation **22-B** suffers from a steric interaction between the *N*(1)-acetyl group and the $C_{13}H_{27}$ side chain as illustrated below. Conformation **22-A** is also reproduced as the minimum energy conformation by the MacroModel program (MM2 and AMBER subroutines) and lies about 4.3 kcal/mol below **22-B**.[10,11]



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Supplementary Material Available: Full experimental details for the preparation of **22** from **5** (10 pages). This information is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) The dibenzyltriazone derivative of alaninal reacted under these conditions to give a 3:1 threo/erythro (anti/syn) mixture of homoallylic alcohols. See ref 5.

(9) Weygand, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437.

(10) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(11) The preference of **22** for the axial-tridecyl conformation **22-A** has been attributed to an intramolecular hydrogen bond between N(1) and N(5)-H (see ref 1). Examination of molecular models suggests that this hydrogen bond would be highly strained.