SYNTHESES OF PROPOSED STRUCTURE OF PSEUDODISTOMIN A TRIACETATE AND ITS REGIOISOMERS ON DIENYL SIDE-CHAIN ¶

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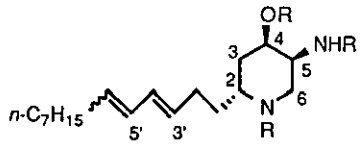
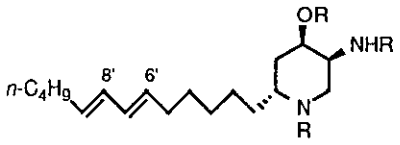
Abstract - The amino alcohol (**5**) was employed as a common starting compound for the synthesis of the piperidines (**1b**), (**14**), and (**16**) with three isomeric tridecadienyl side-chains. The spectral data of the 6'*E*,8'*Z*-diene (**14**) are closely resembled with those of natural pseudodistomin A triacetate.

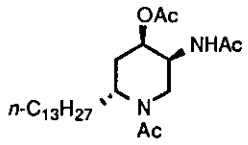
Pseudodistomins A (**1a**) and B (**2a**), potent antineoplastic piperidine alkaloids with calmodulin antagonistic activity, were isolated from the Okinawan tunicate *Pseudodistoma kanoko* as the first piperidine alkaloids from marine sources.[1] Their structures were proposed based only on spectroscopic evidences[1] of uv, ir, ^{1}H- and ^{13}C-nmr and ms. Synthesis[2-5] of tetrahydropseudodistomin triacetate (**4**) has established the basic structure of these two alkaloids together with the absolute stereochemistry of three substituents on the piperidine ring. The structure of pseudodistomin B had been proposed as shown by the structure (**2a**) as having a 3'*E*,5'*E*-dienyl moiety in the side-chain which however was revised to the 6'*E*,8'*E*-geometry (**3a**) by the synthesis of both structures and the degradation reaction of natural pseudodistomin B.[6] Thus interests were directed to pseudodistomin A which was proposed as having a 3'*E*,5'*Z*-dienyl moiety.



1a 5'Z, R=H : Pseudodistomin A
1b 5'Z, R=Ac
2a 5'*E*, R=H : Pseudodistomin B (proposed)
2b 5'*E*, R=Ac



3a R=H : Pseudodistomin B (revised)
3b R=Ac



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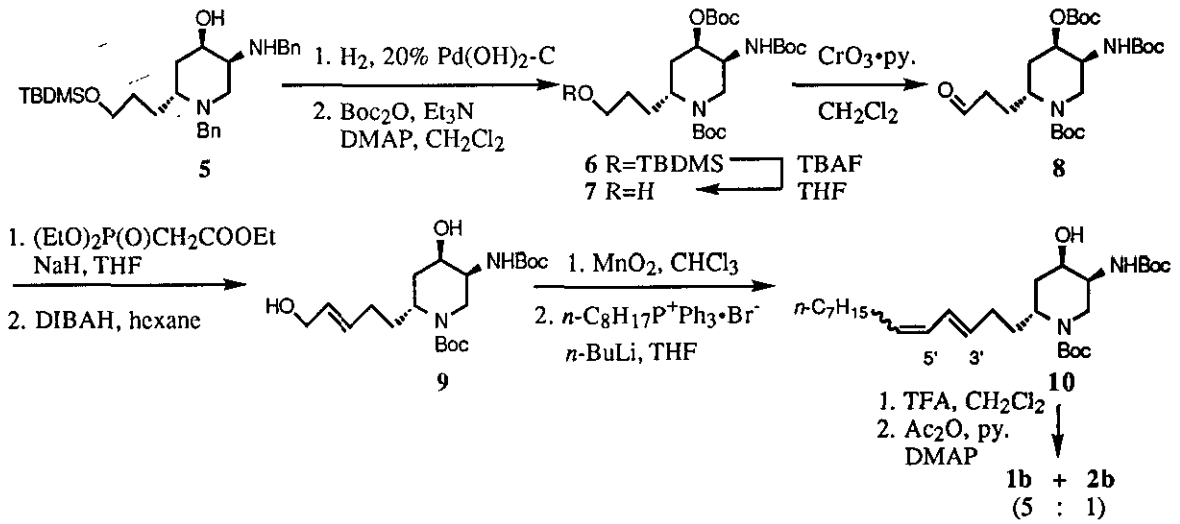
¶ Dedicated to the memory of the late Professor Yoshio Ban.

Here we describe the synthesis of the proposed structure (**1b**) for pseudodistomin A triacetate and its isomeric congeners (**14**) and (**16**) carrying 6'*E*,8'*Z*- and 6'*Z*,8'*E*-dienyl moieties and the result of comparisons of their spectral data with those of natural product.

For the synthesis of a series of isomeric analogs of pseudodistomins with respect to the side-chain, we investigated a stepwise elongation reaction by employing the key intermediate (**5**).[3] According to the conventional methods, the amino alcohol (**5**) was converted to the allyl alcohol (**9**) in six steps. The Wittig reaction of the unstable aldehyde, which was readily prepared from the alcohol (**9**) by oxidation with manganese dioxide, with octylphosphorane in the presence of *n*-butyllithium proceeded smoothly to give a mixture of the 3'*E*,5'*Z*- and 3'*E*,5'*E*-dienes (**10**) in 31% combined yield in two steps from the alcohol (**9**). Without separation, the mixture was subjected to deprotection by treatment with TFA followed by acetylation to give a 5 : 1 mixture of the triacetates (**1b**) and (**2b**) which are isomeric with respect to the geometry at 5'-double bond and separated by hplc. The minor isomer (**2b**) was identical with the known[3] 3'*E*,5'*E*-diene upon direct comparisons of their spectra while the major product (**1b**) was deduced to have the 3'*E*,5'*Z*-dienyl configuration based on the synthetic reaction sequence including the Wittig reaction and thorough assignment of its nmr spectra. Comparison of ^{13}C-nmr data of the isomer (**1b**) with those of pseudodistomin A triacetate[1] showed that they are not identical as shown in Table. Therefore it is clearly drawn the conclusion that pseudodistomin A should have an another structure with respect to the dienyl side-chain.

For the proposal of a revised structure of pseudodistomin A, the consideration of our synthetic work[6] on pseudodistomin B and thorough reassignment of the reported ^{13}C-nmr spectral data were carried out thus



having drawn tentative conclusion that either 6'*E*,8'Z- or 6'Z,8'*E*-dienyl structure could be the one for the alkaloid. In order to synthesize a pair of 6',8'-dienyl analogs, we chose the coupling reaction of a common intermediary tosylate (**11**) with the Grignard reagent including the corresponding dienyl moieties (**12**) and (**13**) for the construction of tridecadienyl side-chains. According to the literatures, (*E*,*Z*)[7]- and (*Z*,*E*)[8]-3,5-decadienol were prepared stereoselectively and then converted to the corresponding bromides (**12**) and (**13**) by treatment with triphenylphosphine and carbon tetrabromide. The coupling reaction[9] of the tosylate (**11**) with (*E*, *Z*)- and (*Z*, *E*)-3,5-decadienylmagnesium bromides prepared from **12** and **13** in the presence of dilithium tetrachlorocuprate proceeded smoothly at -20°C to give a *ca* . 3 : 2 mixture of the acetates (**14**) and (**16**) and the corresponding alcohols (**15**) and (**17**) in 55-66% yields. Acylation of the alcohols (**15**) and (**17**) with acetic anhydride and pyridine gave the acetates (**14**) and (**16**) respectively. Comparisons of ^{1}H- and ^{13}C-nmr spectral data of synthetic dienes (**14**) and (**16**) with those of the authentic pseudodistomin A triacetate[1] have shown that the spectral data of the 6'*E*,8'Z-diene (**14**) are closely resembled with those of the authentic pseudodistomin A triacetate except two signals as shown in Table. It is now impossible to resolve pseudodistomin A enigma from the fact[10] that the natural alkaloid is not available from marine sources and not subjected to reinvestigation of the structure determination.

In conclusion, we have now succeeded in the syntheses of the 3'*E*,5'Z- (**1b**), 6'*E*,8'Z- (**14**) and 6'Z,8'*E*-dienes (**16**), of which **1b** was not identical with natural product though it was the proposed structure. The spectral data of the compound (**14**) with 6'*E*,8'Z-dienyl moiety are closely resembled with those of natural product. We are now extensively working on the synthesis of all the plausible analogs of pseudodistomins with respect to the dienyl structure.

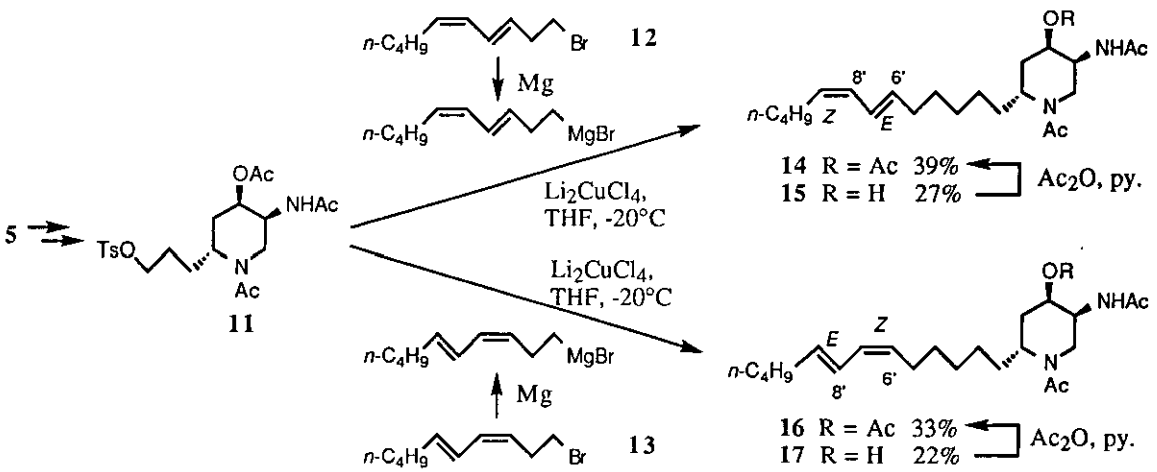


Table Comparisons of ^{13}C-Nmr Data of Synthetic Dienes (**1b**), (**14**), and (**16**) with Authentic Pseudodistomin A Triacetate in $CDCl_3$

carbon		natural (100 MHz)[1]	synthetic (125 MHz)					
			3'*E*, 5'Z (**1b**)		6'*E*, 8'Z (**14**)		6'Z, 8'*E* (**16**)	
		δ	δ	Δ	δ	Δ	δ	Δ
	2	47.5	47.3	-0.2	47.6	0.1	47.6	0.1
piperidine	3	28.2	28.4	0.2	28.4	0.2	28.4	0.2
skeleton	4	66.9	66.8	-0.1	66.9	0	66.9	0
	5	46.8	47.0	0.2	47.2	0.4	47.2	0.4
	6	43.8	43.8	0	43.7	-0.1	43.7	-0.1
		13.8	14.0	0.2	14.0	0.2	14.0	0.2
		22.2	22.6	0.4	22.3	0.1	22.3	0.1
		26.1	27.7	1.6	26.2	0.1	26.2	0.1
		27.3	29.2	1.9	27.4	0.1	27.6	0.3
		28.8	29.2	0.4	29.0	0.2	29.0	0.2
		29.1	29.2	0.1	29.2	0.1	29.6	0.5
side-chain		30.1	29.6	-0.5	30.2	0.1	30.2	0.1
		31.8	29.7	-2.1	31.9	0.1	31.6	-0.2
		32.6	31.8	-0.8	32.8	0.2	32.6	0
		125.8	126.5	0.7	125.9	0.1	125.6	-0.2
		128.4	128.1	-0.3	128.6	0.2	128.9	0.5
		130.1	131.0	0.9	130.3	0.2	129.7	-0.4
		134.0	132.3	-1.7	134.3	0.3	134.9	0.9

The underlines show that difference of the chemical shifts between synthetic dienes with natural pseudodistomin A triacetate is over 0.3 ppm.

ACKNOWLEDGMENTS

We are grateful to Professor J. Kobayashi, Hokkaido University (Japan), for providing ir, ^{1}H-nmr and ^{13}C-nmr spectral data of pseudodistomin A triacetate. Thanks are also extended to the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grant.

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Received, 17th July, 1995