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Synthesis and NMR Profiling of Dioxabicyclo[3.2.1]octanes Related to Pinnatoxin D. Confirmation of the Relative Stereochemistry about Rings E and F

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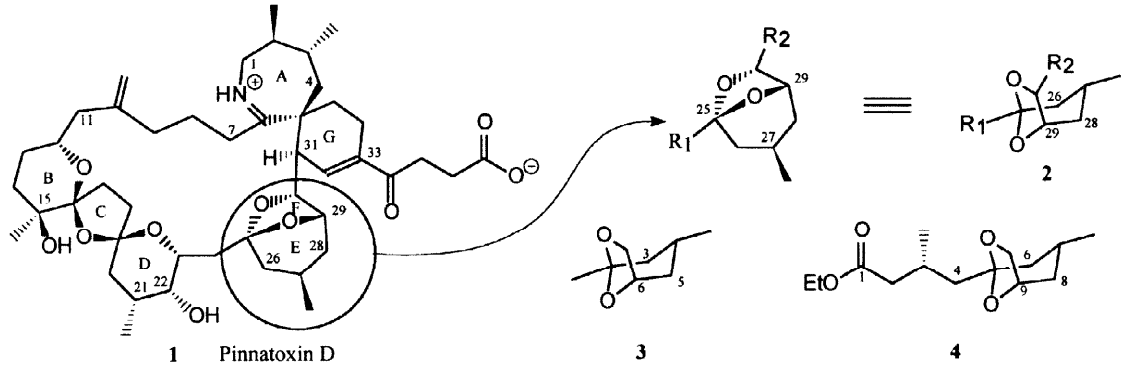
Abstract: Bicyclic ketals **3** and **4** were synthesised as models to confirm the proposed stereochemistry of the bicyclic ketal system (rings E,F) of the shellfish toxin pinnatoxin D. The key step is a stereoselective cyclisation of dihydroxyketones to provide the bicyclic structure.

The pinnatoxins are a group of potent marine toxins implicated as the causative agents in human food poisoning resulting from ingestion of shellfish from the *Pinna* genus.[1] The four pinnatoxins, A-D, described to date, incorporate an iminium function in a spirocyclic system along with trioxadispiro- and bicycloketal sub-structures within an overall polyether macrolide assembly. Uemura and coworkers have reported the relative stereochemistry of pinnatoxins A[2] and D[3] based on extensive NMR measurements, and very recently a stereocontrolled construction of the B,C,D trioxadispiro fragment of pinnatoxins A-C was described.[4] Pinnatoxin D, **1** unlike A-C, bears substituents on the D ring (*cis* C22 hydroxyl and C21 methyl group), and possesses a more elaborate sidechain at C33, but lacks a C28 hydroxyl in the E ring. The pinnatoxins have certain structural resemblances to the spirolides B and D, isolated from the digestive glands of mussels and scallops.[5]



1 Pinnatoxin D **3** **4**

In connection with ongoing synthetic work in the polycyclic ketal area,[6] we have acquired two dioxabicyclo[3.2.1]octanes **3** and **4** of known absolute stereochemistry, that resemble structurally the E,F bicyclic system of pinnatoxin D **1**. For comparison with these model compounds, the E,F system is excised from **1** and shown as **2** above. Our structure searching reveals that arrangement **2**, even when both R_1 and R_2 = H, is represented naturally only by pinnatoxin D, **1**. Full determinations of ^1H and ^{13}C NMR chemical shifts and *vicinal* proton-proton coupling constants are now reported for **3** and **4**, and for the relevant PC-model derived structures.[7] Comparisons of these data with those reported, confirm the nature and stereochemistry of the sub-structure **2** of pinnatoxin D **1**.

Model structures **3** and **4** were derived (Scheme 1) from protected enone **6** which was acquired from *R*-(+)-pulegone **5**.[8] Treatment of **6** with AD-mix-α and protection of the formed diol (*bis*-benzylation), followed by ketone release, yielded **7**. On hydrogenation (Pd/C) in methanol, **7** afforded the desired

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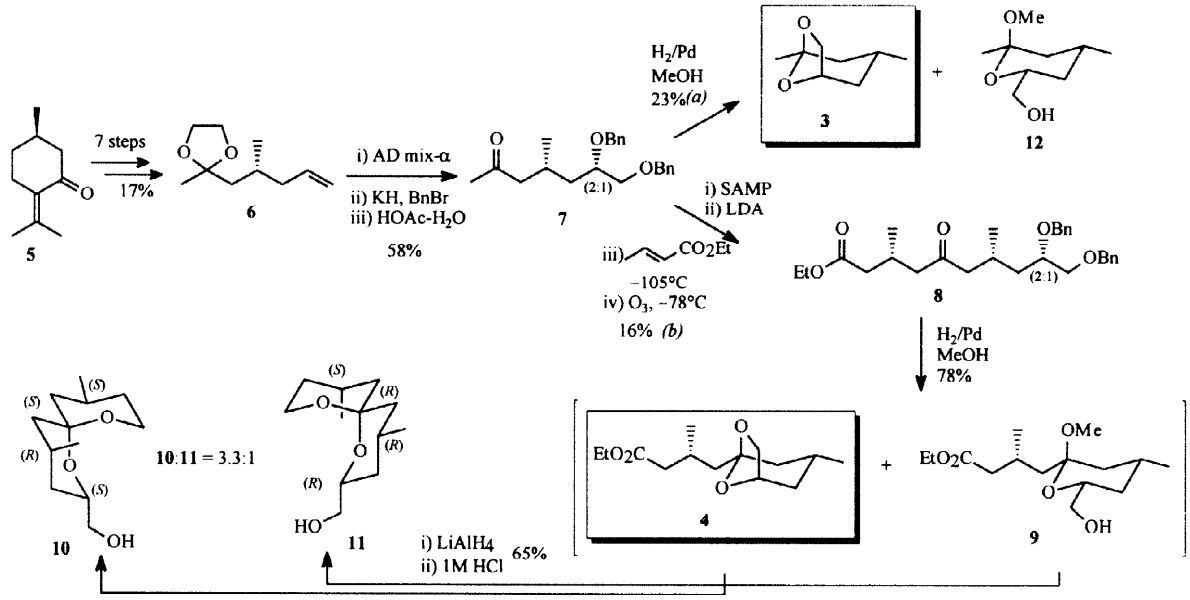
bicyclo[3.2.1]octane **3**, as well as methyl ketal **12**, reflecting the moderate 2:1 induction level in the dihydroxylation step.[9]

Alternatively, the SAMP derivative ((S)-1-amino-2-methoxymethylpyrrolidine) of **7**, was deprotonated and added to ethyl crotonate at -105°, followed by ozonolytic removal of the hydrazone.[10] Various measurements indicated a very high level (> 99.5%) of induction in the conjugate addition step, so that **8** was essentially still a 2:1 diastereomeric mixture epimeric at the secondary alcohol centre. Debenzylation by hydrogenolysis (in MeOH) provided a mixture of desired dioxabicyclo[3.2.1]octane **4**[11] and the monocyclic methyl ketal **9**. Reduction of the **4/9** mixture followed by acidic workup, led to a mixture of spiroacetals **10** and **11** which were obtained in a 3.3:1 ratio after separation by flash chromatography.[12] Some preferential loss of the more polar **9** occurred during workup following debenzylation, and this resulted in a relative increase in the proportion of **10**. Detailed NMR studies confirmed the relative (and hence absolute) stereochemistry of **10** and **11** and therefore of **4** and **9**.



(a) Losses were experienced due to the volatility of these compounds. *(b)* Not optimised. Side-reactions of the benzyl ethers apparently intervened under these conditions.

Scheme 1

A full listing of the ^{1}H and ^{13}C chemical shifts for **3** and **4** and the dioxabicyclo[3.2.1]octane substructure **2** of pinnatoxin D is shown in Table 1. There is very good agreement for the ^{1}H and ^{13}C shifts between the three systems, when positions uninfluenced by side chain differences are compared.

These considerations are less likely to influence significantly the ^{1}H-^{1}H coupling constants, and in Table 2 are located the observed and calculated (PC model) *vicinal* (^{3}J) coupling constants for **3** and **4**, as well as those reported for **2**.[3] The agreement between observed and calculated coupling constants for **3** and **4** is exceptionally good, but because pinnatoxin D bears an alkyl group at C30, we also modelled the arrangement with a methyl group at this position (Model 1, Table 2). This causes a geometrical change, with a correspondingly smaller $J_{H7\text{-}H6}$ (now 4.1 from 6.5 Hz), in good agreement with the value (4.5 Hz) reported for **2**.[3] Otherwise there is excellent agreement between the natural system **2** and the models **3** and **4**. Inverting the stereochemisty at C_{27}, so that the methyl group is *axial* (Model 2, Table 2), profoundly perturbs the calculated coupling constants, and agreement with the values for **2**, **3** and **4** is now of a much lower order.

Consequently, it is clear that the assignments and relative stereochemistry deduced for the E,F ring portion of pinnatoxin D are correct and very adequately modelled by the smaller structures described herein. In addition, the synthetic approaches to **3** and **4** may be optimized and adjusted to provide an intermediate for linking to rings D and G in an overall synthesis of pinnatoxin D.

Table 1

Comparisons[a] of Chemical Shifts for **2**, **3** and **4**

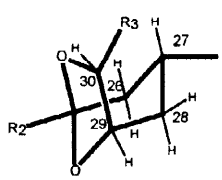
2		**3**			**4**		
	CD_3OD		*C_6D_6*	**CD_3OD**		*$CDCl_3$*	**CD_3OD**
$H26_{ax}$	**1.44**	$H3_{ax}$	*1.11*	**1.21**	$H6_{ax}$	*1.19*	**1.18**
$H26_{eq}$	**1.94**	$H3_{eq}$	*1.62*	**1.74**	$H6_{eq}$	*1.70*	**1.70**
H27	**2.25**	H4	*1.80*	**2.00**	H7	*2.02*	**2.03**
$H28_{ax}$	**1.64**	$H5_{ax}$	*1.19*	**1.35**	$H8_{ax}$	*1.39*	**1.36**
$H28_{eq}$	**2.08**	$H5_{eq}$	*1.09*	**1.64**	$H8_{eq}$	*1.54*	**1.64**
H29	**4.80**	H6	*4.11*	**4.51**	H9	*4.48*	**4.51**
H30	**3.98**	H7'	*3.63*	**3.75**	H10'	*3.75*	**3.72**
Me39	**1.01**	Me8	*0.71*	**0.90**	Me11	*0.88*	**0.90**
C25	**110.6**	C2	*106.95*	**108.26**	C5	*108.38*	**109.62**
C26	**45.0**	C3	*44.78*	**45.37**	C6	*43.54*	**44.81**
C27	**26.0**	C4	*24.12*	**24.36**	C7	*23.73*	**24.89**
C28	**33.6**	C5	*37.26*	**37.94**	C8	*37.25*	**38.21**
C29	**77.1**	C6	*74.68*	**76.20**	C9	*74.53*	**76.00**
C30	**80.1**	C7	*69.03*	**69.91**	C10	*68.73*	**69.75**
C39	**22.7**	C8	*21.59*	**21.75**	C11	*21.46*	**21.88**

(a) Corresponding protons and carbons in **2**, **3** and **4** are located in horizontal rows

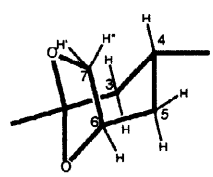
Table 2

Comparison of Vicinal Coupling Constants[a,b,c]

2		**3**			**Model 1**		**4**			**Model 2**	
	Obs		**Obs**	Calc		Calc		**Obs**	Calc		Calc
H30-H29	**4.5**	H7'-H6	**5.4**	6.5	H7-H6	4.1	H10'-H9	**5.1**	6.4	H7-H6	3.9
H29-H28ax	**3.0**	H6-H5ax	**3.0**	3.8	H6-H5ax	4.1	H9-H8ax	**3.1**	3.7	H6-H5ax	5.4
H29-H28eq	**2.3**	H6-H5eq	**2.2**	2.3	H6-H5eq	2.3	H9-H8eq	**1.9**	2.6	H6-H5eq	1.6
H27-H28ax	**10.0**	H4-H5ax	**11.9**	11.6	H4-H5ax	10.9	H7-H8ax	**11.9**	11.3	H4-H5ax	8.4
H27-H28eq	**4.0**	H4-H5eq	**5.3**	5.3	H4-H5eq	5.9	H7-H8eq	**5.1**	5.5	H4-H5eq	1.0
H27-H26ax	**10.0**	H4-H3ax	**11.4**	11.7	H4-H3ax	11.2	H7-H6ax	**11.4**	11.3	H4-H3ax	8.0
H27-H26eq	**5.5**	H4-H3eq	**5.7**	5.3	H4-H3eq	5.7	H7-H6eq	**5.4**	5.4	H4-H3eq	1.0



2
(From Pinnatoxin D)



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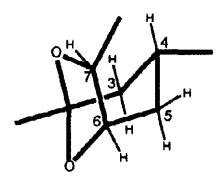
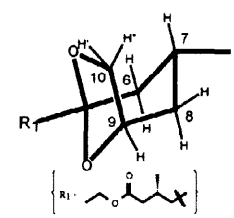
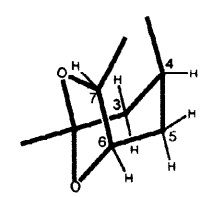


Model 1



4



Model 2

(a) Observed coupling constants listed for **2**[3], **3** and **4** pertain to CD_3OD as solvent.

(b) In **Model 1**, CH_3 replaces H7" of **3**. In **Model 2**, configuration at C4 is inverted.

(c) Vicinal couplings to H7" in **3** and H10" in **4** are very small (<1Hz), and are not listed. There is no corresponding coupling in **2**, as this position bears a side-chain in the natural product.

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References and Notes:

1. Uemura, D.; Chou, T.; Hains, T.; Nagatsu, A.; Fukuzawa, S.; Zhang, S. Chen, H. *J.Am.Chem.Soc.*, **1995**,*117*, 1155.
2. Chou, T.; Kams, O.; Uemura, D. *Tetrahedron Lett.*, **1996**, *37*, 4023.
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5. Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Watson-Wright, W. M.; Wright, J. L. C. *J.Chem.Soc.,Chem.Commun*, **1995**, 2159, and references therein. See also Jacobs, M. F.; Kitching, W. *Current Organic Chemistry*, **1998**, *2*(No.4), In Press.
6. Suthers, B. D.; Kitching, W. Unpublished Work.
7. For molecules of this complexity containing C,H,O only, this approach would yield geometries and coupling constants very similar to those based on MM3 modelling, and valid for our purposes.
   The Assignment of H10" in **4** was confirmed by NOE observed across the ring from H7.
8. Tu, Y. Q.; Moore, C. J.; Kitching, W. *Tetrahedron: Asymmetry*, **1995**, *6(2)*, 397, and references therein.
9. Compound **3**: **HR-EIMS** m/z 142.0998 (M^+). Calcd. for $C_8H_{14}O_2$, 142.0994.
   EIMS m/z (%); 143(0.2); 142(2.2); 127(0.7); 113(0.3); 12(1.2); 101(1.7); 100(11); 97(2.4); 85(1.5); 84(2.4); 83(1.9);82(8.8); 81(2.7); 67(10); 58(10); 55(4.0); 43(100); 41(20); 39(11).
   $[\alpha]_D^{25} = -37^o$ (c=0.05 C_6D_6). This rotation is approximate, due to volatility and low concentration.
   The key ^1H and ^{13}C NMR data are located in Tables 1 and 2.
10. See Enders, D.; Papadopoulos, K.; Rendenbach, B. E. M.; *Tetrahedron Lett.*, **1986**, *27*, 3491.
11. Compound **4**: **HR-EIMS** m/z 256.1684 (M^+). Calcd. for $C_{14}H_{24}O_4$, 256.1675.
   EIMS m/z(%); 241(1.0); 212(2.8); 211(13); 193(0.9); 175(1.2); 169(6.6); 168(2.7); 158(11); 157(100); 142(3.9);130(4.1); 129(54); 127(9.4); 112(8.6); 101(27); 100(11);83(11); 69(38); 67(19); 59(12); 55(29); 43(33); 42(26); 41(64).
   $[\alpha]_D^{25} = -46°$ (c=2.32 pentane).
   The key ^1H and ^{13}C NMR data are located in Tables 1 and 2.
12. Compound **10**: **HR-EIMS** m/z 214.1566 (M^+). Calcd. for $C_{12}H_{22}O_3$, 214.1569.
   EIMS m/z(%) 215(0.3); 214(0.5); 199(1.5); 185(0.3); 184(4.6); 183(34); 169(3.4); 165(4.0); 157(2.6); 145(23); 139(42); 127(24); 115(78); 112(16); 111(26); 97(14); 84(30); 81(30); 73(32); 71(13); 69(75); 67(19); 57(19); 55(55);43(60); 42(36); 41(100); 39(35).
   $[\alpha]_D^{25} = +73°$ (c=0.22 pentane).
   ^1H NMR 400MHz (C_6D_6; J in Hz) δ 0.73 (3H,d,J=6.6;Me14); 0.93 (1H,dd,J=12.7,12.6;$H11_{ax}$); 0.98-1.06 (2H,m;$H3_{eq}$,$H9_{ax}$); 1.18 (1H,dm,J=13.0;$H9_{eq}$); 1.21 (3H,d,J=7.3;Me13); 1.39 (1H,ddd,J=13.1,1.6,5.6;$H3_{ax}$); 1.41 (1H,dd,J=13.7,5.6;$H5_{ax}$); 1.45 (1H,ddd,J=13.7,3.5,1.2;$H5_{eq}$); 1.53 (1H,ddd,J=13.0,3.9,1.8;$H11_{eq}$); 1.74-1.89 (3H,m;OH,H4,H10); 3.43-3.53 (3H,m;H12',H12'',$H8_{eq}$); 3.59 (1H,dd,J=12.6,11.2,2.4;$H8_{ax}$); 3.85 (1H,ddddd,J=11.5,6.7,3.8,2.9,0.5;H2).
   ^{13}C NMR 100MHz (C_6D_6) δ 21.03(C14); 22.40(C13); 25.17(C10 or C4); 25.18(C4 or C10); 32.48(C3); 33.96(C9); 40.90(C5); 44.95(C11); 60.27(C8); 65.65(C2); 66.64(C12); 97.13(C6).
   Compound **11**: **HR-EIMS** m/z 214.1563 (M^+). Calcd. for $C_{12}H_{22}O_3$, 214.1569.
   EIMS m/z(%) 214(0.6); 199(0.7); 185(0.4); 184(3.7); 183(27); 165(2.9); 145(18); 142(6.5); 139(32); 127(18);115(100); 113(12); 111(18); 99(6.6); 97(15); 84(22); 81(19); 73(40); 69(63); 67(16); 55(43); 43(45); 42(24); 41(68); 39(23).
   $[\alpha]_D^{25} = -58°$ (c=0.24 pentane).
   ^1H NMR 400MHz (C_6D_6; J in Hz) δ 0.71-0.79 (5H,m;$H5_{ax}$,$H3_{ax}$,Me13; incl δ 0.75(3H,d,J=6.6;Me13)); 0.98-1.06 (4H,m;$H9_{ax}$,Me14; incl δ 1.02(3H,d,J=7.0;Me14)); 1.18 (1H,dm,J=12.7;$H3_{eq}$); 1.35 (1H,ddd,J=13.6,5.9,1.0;$H11_{ax}$ or $H11_{eq}$); 1.50 (1H,dd,J=13.2,5.3;$H11_{eq}$ or $H11_{ax}$); 1.52 (1H,dq,J=17.7,4.6;$H9_{eq}$); 1.61-1.72 (3H,m;OH,H10,$H5_{eq}$; incl δ 1.69(1H,ddd,13.2,3.8,1.8;$H5_{eq}$)); 1.94 (1H,tqt,J=12.1,6.5,3.9;H4); 3.31 (1H,dt,J=11.6,4.9;$H8_{eq}$); 3.40-3.53 (2H,m;H12',H12''); 3.75 (1H,dddd,J=11.5,9.3,3.5,0.4;$H8_{ax}$); 3.85 (1H,dddd,J=11.7,6.5,3.7,2.4;H2).
   ^{13}C NMR 100MHz (C_6D_6) δ 21.14(C14); 22.26(C13); 24.77(C4); 25.49(C10); 31.81(C9); 5.38(C3); 42.13(C11); 42.51(C5); 57.85(C8); 66.36(C12); 70.81(C2); 97.28(C6).