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Stereoselective Synthesis of 2,3-Dihydroxy-4-dimethylamino-5-methoxypentanoic Acid, A Fragment of Calyculins ------- Determination of the Absolute Configuration of Calyculins[1]

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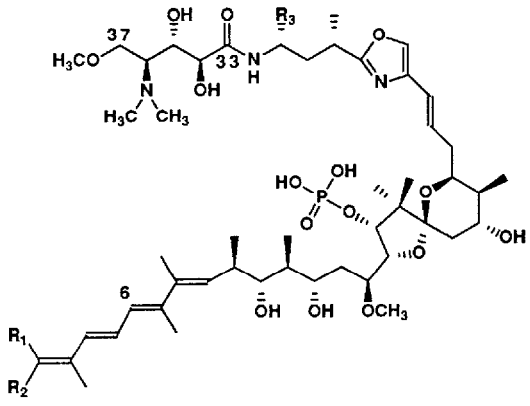
Abstract 2,3-Dihydroxy-4-dimethylamino-5-methoxypentanoic acid (**2**) with (2R,3R,4R)-configuration has been stereoselectively prepared from (S)-pyroglutaminol (**3**) and revealed to be the enantiomer of the compound derived from calyculins (**1**), which provides the conclusive evidence on the absolute configuration of calyculins

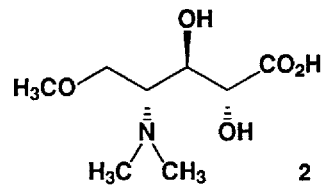
Calyculins, isolated from the marine sponge *Discodermia calyx*,[2] have unique structures shown in **1** as well as intriguing biological activities, e g , cytotoxicity, antitumor activity,[2] inhibition of protein phosphatases,[3] etc Attempts to synthesize calyculins have been actively undertaken by several groups [4]

The structures of calyculins have been established by X-ray diffraction and spectral studies except their absolute configuration [2] Very recently, Matsunaga and Fusetani have disclosed[5] that hydrolysis of a mixture of calyculins A, B, E, and F afforded 2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid, the C_{33}-C_{37} portion of calyculins, which has been revealed to have (2S,3S,4S)-configuration by the CD spectral studies, and hence the absolute configuration of calyculins should be depicted as the structures **1**



Calyculins (1)

	R_1	R_2	R_3		
A	CN	H	H	E	6Z isomer of A
B	H	CN	H	F	6Z isomer of B
C	CN	H	CH_3	G	6Z isomer of C
D	H	CN	CH_3	H	6Z isomer of D



2

We now wish to report a stereoselective synthesis of 2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid (**2**) with (2R,3R,4R)-configuration, which unambiguously determines the absolute configuration of calyculins (**1**)

The synthesis commenced with (S)-pyroglutaminol (**3**),[6] which was treated with p-methoxybenzyl chloride (MPMCl) under basic conditions to give the bis-MPM-pyrrolidinone **4**, mp 58 5-59 5 °C, $[\alpha]_D^{24}$ +32 2° (c 1 25, $CHCl_3$), as shown in Scheme 1 Selective removal of the O-MPM function with DDQ[7] followed by methylation afforded the methoxy derivative **5** as a colorless oil, $[\alpha]_D^{24}$ +85 5° (c 1 2, $CHCl_3$) Successive treatment of **5** with lithium diisopropylamide (LDA), PhSeCl, and hydrogen peroxide[8] yielded the α, β-unsaturated lactam **6** as a colorless oil, $[\alpha]_D^{24}$ -10 4° (c 2, $CHCl_3$) cis-Dihydroxylation via catalytic osmylation followed by acetonide formation furnished the acetonide **7**, mp 74-75 °C, $[\alpha]_D^{26}$ +40 6° (c 0 5, $CHCl_3$), as a single diastereoisomer Apparently, attack of osmium tetroxide has mainly occurred from the opposite side to the methoxymethyl group [8,9] Removal of the N-MPM moiety of **7** was accomplished by use of ceric ammonium nitrate (CAN),[10] while trifluoroacetic acid[11] as well as the electrochemical method[12] was not effective at all The deprotected product **8** was treated with di-tert-butyl dicarbonate (Boc_2O) to give the required Boc derivative **9** as a yellow oil, $[\alpha]_D^{24}$ -92 3° (c 1, $CHCl_3$) Hydrolytic ring-cleavage with lithium hydroxide followed by methyl esterification with trimethylsilyldiazomethane ($TMSCHN_2$)[13] quantitatively afforded the ester **10** Although selective removal of the Boc function easily proceeded with trimethylsilyl triflate (TMSOTf), neutralization after the reaction furnished the cyclized product **8** instead of the required amino acid methyl ester **11** However, after hydrolytic ring-cleavage of **9**, treatment with benzylamine in the presence of diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$)[14] and triethylamine afforded the benzylamide **12**, mp 122-123 °C, $[\alpha]_D^{23}$ +26° (c 0 56, $CHCl_3$), in 78% yield The benzylamide **12** smoothly underwent (1) removal of the Boc group with TMSOTf, (2) catalytic, reductive N,N-dimethylation, and (3) reprotection of the diol as the acetonide, giving the N,N-dimethyl benzylamide **13** as a colorless oil, $[\alpha]_D^{24}$ +50 5° (c 0 52, $CHCl_3$), in 83% yield Final acid hydrolysis afforded (2R,3R,4R)-2,3-dihydroxy-4-dimethylamino-5-pentanoic acid (**2**), mp 95-99 °C, $[\alpha]_D^{22}$ +36° (c 0 09, EtOH-H_2O/1 1) Its ^{1}H-NMR spectrum was completely identical with that of the sample from calyculins,[5] but the sign of the specific rotation[15] and the Cotton effect curve of the CD spectrum were reversed

This synthesis provides not only the conclusive evidence on the absolute configuration of calyculins (**1**) but also an efficient entry into the total synthesis of the biologically interesting calyculins (**1**)

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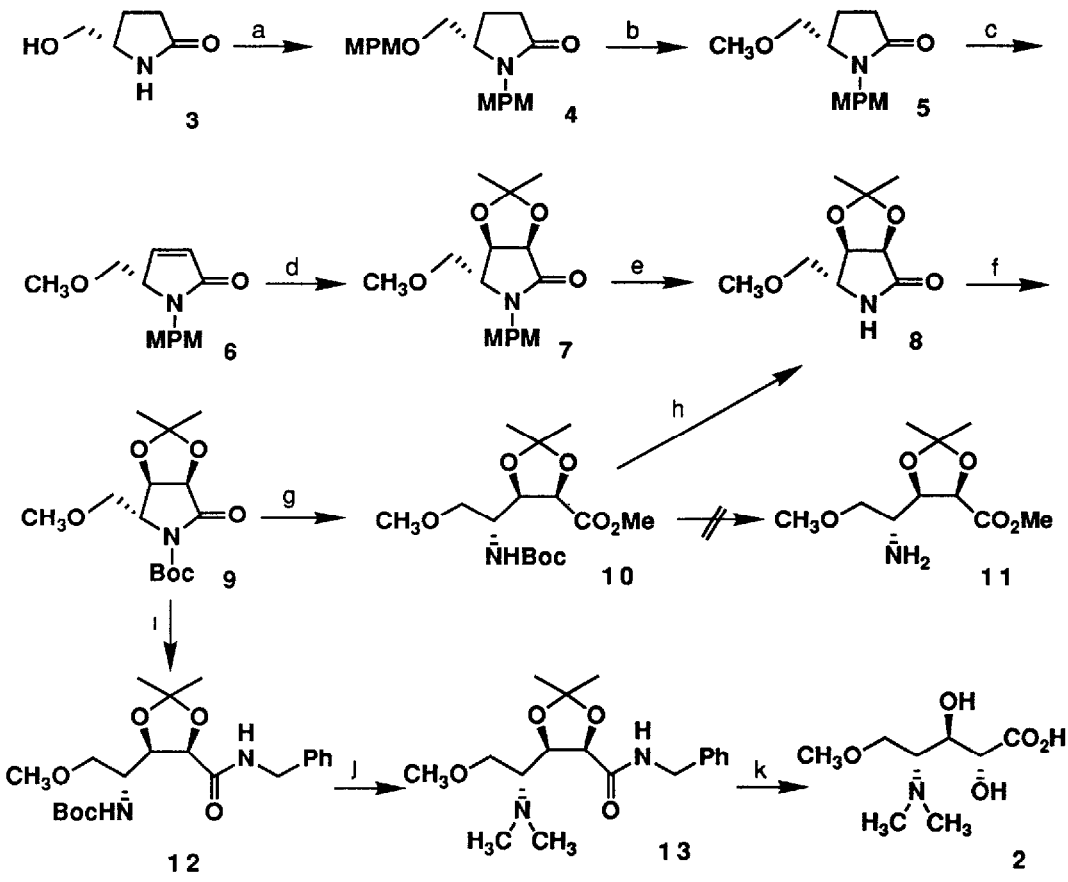

Scheme 1

a) MPMCl, NaH, DMSO, rt, 24h, 73% b) DDQ, CH_2Cl_2-H_2O (19 1), rt, 4h, CH_3I, NaH, THF, rt, 1h, 75% c) LDA, THF, -78°C, 30mın, PhSeCl, -78°C, 30mın, 30% aq H_2O_2, EtOAc, rt, 30mın, 49% d) OsO_4, N-methylmorpholine N-oxide, toluene-acetone-water, rt, 12 5h, 2,2-dımethoxypropane, p-TsOH H_2O, rt, 5h, 67% e) CAN, CH_3CN-H_2O (7 3), 0°C, 20mın then rt, 1 5h f) Boc_2O, 4-(N,N-dımethylamıno)pyrıdıne, CH_3CN, rt, 10h, 45% from **7** g) LıOH, THF-H_2O, 0°C, 30mın, $TMSCHN_2$, benzene-methanol, quant h) TMSOTf, CH_2Cl_2, 0°C, 1h, aq $NaHCO_3$, 83% ı) LıOH, THF-H_2O, 0°C, 30mın, $PhCH_2NH_2$, DPPA, Et_3N, DMF, 0°C, 1h then rt, 41h, 78% j) TMSOTf, CH_2Cl_2, 0°C, 1h, 37% aq HCHO, AcOH, 5% Pd-C, H_2, MeOH, rt, 60h, 2,2-dımethoxypropane, p-TsOH H_2O, rt, 3h, 83% k) 6N aq HCl, MeOH, 130°C, 1 5h, 58%

References and Notes

1 New Methods and Reagents in Organic Synthesis 96

2 (a) Kato, Y , Fusetani, N , Matsunaga, S , Hashimoto, K , Fujita, S , Furuya, T *J Am Chem Soc* **1986**, *108*, 2780 (b) Kato, Y , Fusetani, N , Matsunaga, S , Hashimoto, K , Koseki, K *J Org Chem* **1988**, *53*, 3930 (c) Matsunaga, S , Fujiki, H , Sakata, D , Fusetani, N *Tetrahedron* **1991**, *47*, 2999

3 (a) Ishihara, H , Martin, B L , Brautigan, D L , Karaki, H , Ozaki, H , Kato, Y , Fusetani, N , Watabe, S , Hashimoto, K , Uemura, D , Hartshorne, D J *Biochem Biophys Res Commun* **1989**, *159*, 871 (b) Suganuma, M , Fujiki, H , Furuya-Suguri, H , Yoshizawa, S , Yasumoto, S , Kato, Y , Fusetani, N , Sugimura, T *Cancer Res* **1990**, *50*, 3521

4 (a) Hara, O , Nakao, K , Tanada, Y , Nishio, A , Matsubara, J , Yokokawa, F , Hamada, Y , Shioiri, T *Tennen Yukikagobutsu Toronkai Koenyoushishu* **1990**, *32*, 617 (b) Hara, O , Hamada, Y , Shioiri, T *Synlett* **1991**, 283 and 285 (c) Duplantier, A J , Nantz, M H , Roberts, J C , Short, R P , Somfai, P , Masamune, S *Tetrahedron Lett* **1989**, *30*, 7357 (d) Evans, D A , Gage, J R *Tetrahedron Lett* **1990**, *31*, 6129 (e) Zhao, Z , Scarlato, G R , Armstrong, R W *Tetrahedron Lett* **1991**, *32*, 1609

5 Private communication

6 Saijo, S , Wada, M , Himizu, J , Ishida, A *Chem Pharm Bull* **1980**, *28*, 1449

7 (a) Horita, K , Yoshioka, T , Tanaka, T , Oikawa, Y , Yonemitsu, O *Tetrahedron* **1986**, *42*, 3021 (b) For a review, see Yonemitsu, O *J Synth Org Chem Japan*, **1985**, *43*, 691

8 Analogous sequence of reactions has been used for the synthesis of AI-77-B, see Hamada, Y , Kawai, A , Kohno, Y , Hara, O , Shioiri, T *J Am Chem Soc* **1989**, *111*, 1524

9 Cf Ikota, N , Hanaki, A *Chem Pharm Bull* **1989**, *37*, 1087

10 Yoshimura, J , Yamamura, M , Suzuki, T , Hashimoto, H *Chem Lett* **1983**, 1001

11 Smith, A B , III, Rano, T A , Chida, N , Sulikowski, G A *J Org Chem* **1990**, *55*, 1136

12 Fukase, K , Tanaka, H , Torii, S , Kusumoto, S *Tetrahedron Lett* **1990**, *31*, 389

13 Shioiri, T , Aoyama, T , Mori, S *Org Synth* **1990**, *68*, 1 (b) Hashimoto, N , Aoyama, T , Shioiri *Chem Pharm Bull* **1981**, *29*, 1475

14 Shioiri, T , Yamada, S *Org Synth* **1984**, *62*, 187 (b) Shioiri, T , Ninomiya, K , Yamada, S *J Am Chem Soc* **1972**, *94*, 6203

15 The compound **2** of natural origin shows $[\alpha]_D^{23}$ -21° (c 0 07, EtOH-H_2O/1 1) [5]

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