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A Synthesis of the Tetraene Fragment of Calyculins as Its Antipodal Form

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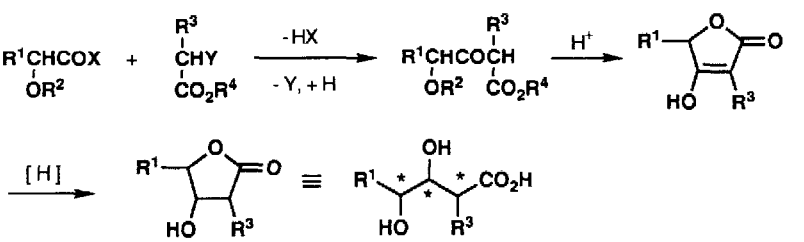
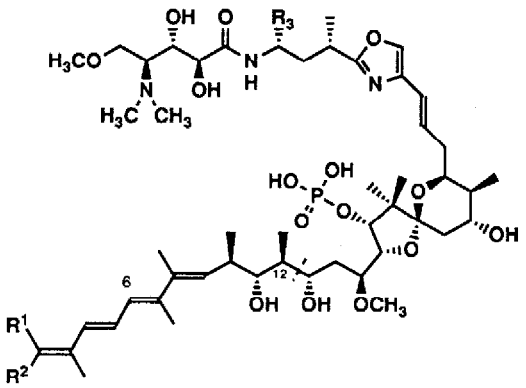
Abstract: The antipodal form **2** of the tetraene fragment, the C1- C12 portion, of calyculins (**1**) has been synthesized by use of the stereoselective hydrogenation of the butenolide **6** followed by the successive Wittig-type chain elongation of the lactol **9** as key steps.

A series of reactions involving the C-acylation of the active methylene or methine compounds with optically active α-hydroxy acids, the butenolide formation under acidic conditions, followed by the stereoselective hydrogenation, outlined below, have now proved to be a useful method for the construction of the optically active hydroxy acids containing three contiguous stereogenic centers.[1]



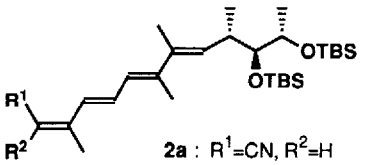
This methodology was recently[1d] applied with success to the synthesis of the C13-C19 fragment of calyculins. Calyculins (**1**) isolated from the marine sponge *Discodermia calyx*[2,3] have strong antineoplastic and/or cytotoxic activity and calyculin A has been revealed to be an inhibitor of protein phosphatases 1 and 2A.[4] We now wish to report the synthesis of the tetraene fragment, the C1-C12 portion, of calyculins as the antipodal form **2** by applying the above synthetic methodology as key steps.

We started the synthesis from O-acetyl (S)-lactic acid (**3**) easily prepared from (S)-lactic acid.[5] Activation of the carboxyl group of **3** with carbonyldiimidazole (CDI) followed by the coupling with magnesium enolate of ethyl hydrogen methylmalonate (**4**) afforded the β-ketoester **5** as an oily diastereoisomeric mixture



Calyculins (1)

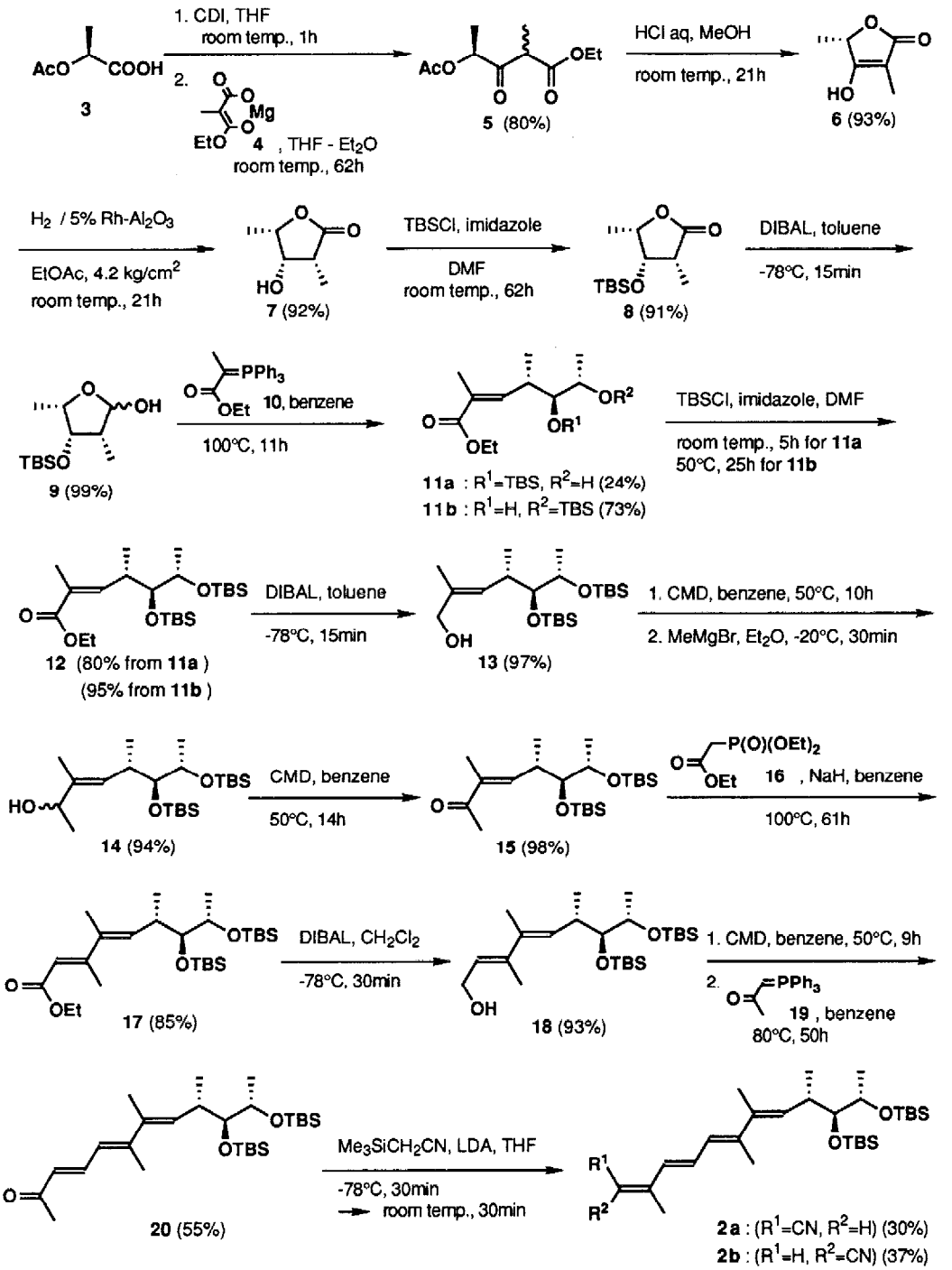
	R^1	R^2	R^3	
A	CN	H	H	**E** : 6Z isomer of **A**
B	H	CN	H	**F** : 6Z isomer of **B**
C	CN	H	CH_3	**G** : 6Z isomer of **C**
D	H	CN	CH_3	**H** : 6Z isomer of **D**



2a : R^1=CN, R^2=H
2b : R^1=H, R^2=CN
TBS : $Bu^t(Me)_2Si$ -

in 80% yield. Acidic treatment of **5** gave the butenolide **6** as a colorless solid, mp 127-129°C, $[\alpha]^{25}_D$ +23.4° (c 1, MeOH), in 93% yield. Catalytic hydrogenation over 5% rhodium-alumina in ethyl acetate (4.2 kg/cm^2, room temp., 21 h) stereoselectively proceeded to furnish the γ-lactone **7** as a colorless oil in 92% yield. After protection of the alcoholic function of **7** with tert-butyldimethylsilyl chloride (TBSCl), the resulting TBS derivative **8**, mp 61-62°C, underwent the reduction with diisobutylaluminum hydride (DIBAL) to give the required furanoside **9** as a colorless oil, $[\alpha]^{23}_D$ -23.4° (c 1.1, MeOH), in almost quantitative yield. The Wittig homologation of **9** with the phosphorane **10** was accompanied with the migration of the TBS group to give a mixture of the oily mono TBS derivatives **11a** ($[\alpha]^{23}_D$ -29.8° (c 1.1, MeOH), in 24% yield and **11b** ($[\alpha]^{23}_D$ -23.7° (c 1.3, MeOH), in 73% yield.[6] Silylation of **11a** with TBSCl smoothly proceeded under the standard conditions (room temp., 5 h) while the silylation of **11b** required the forcing conditions (50°C, 25 h). The di-TBS derivative **12** was obtained as a colorless oil, $[\alpha]^{23}_D$ -34.0° (c 1, MeOH), in 80 and 95% yields, respectively. Reduction of **12** with 2 equivalents of DIBAL afforded the alcohol **13** as a colorless oil, $[\alpha]^{23}_D$ -14.3° (c 1.2, MeOH), in 97% yield. Oxidation of the alcohol **13** to the corresponding aldehyde was conveniently achieved by use of chemical manganese dioxide (CMD) produced for battery.[7] The crude aldehyde underwent the Grignard reaction with methylmagnesium bromide to give a 3 : 2 mixture of the alcohol **14** as a colorless oil, $[\alpha]^{23}_D$ -28.5°C (c 1, MeOH), in 94% yield in two steps. Oxidation of the mixture with CMD afforded the α,β-unsaturated ketone **15** as a colorless oil, $[\alpha]^{23}_D$ -31.7° (c 1.3, MeOH), in 98% yield.

Conversion of **15** to **2** was rather straightforward. Two carbon homologation of **15** was achieved by the Horner-Emmons reaction with the sodium salt of the phosphonate **16**, giving the dienylester **17** as a colorless oil, $[\alpha]^{23}_D$ -44.2° (c 1.3, MeOH), in 85% yield accompanied with the recovery of the starting α,β-unsaturated ketone **15** in 8% yield. DIBAL reduction of the ester **17** afforded the alcohol **18** in 93% yield. Oxidation of the alcohol **18** with CMD furnished the aldehyde, which was stereoselectively converted to the trienone **20** as a pale yellow oil in 55% yield by the Wittig reaction with the ketophosphorane **19**. The Peterson olefination of **20**


1. CDI, THF
room temp., 1h
2.
4 , THF - Et2O
room temp., 62h
3
5 (80%)
HCl aq, MeOH
room temp., 21h
6 (93%)
H2 / 5% Rh-Al2O3
EtOAc, 4.2 kg/cm2
room temp., 21h
7 (92%)
TBSCl, imidazole
DMF
room temp., 62h
8 (91%)
DIBAL, toluene
-78°C, 15min
9 (99%)
10, benzene
100°C, 11h
11a : R1=TBS, R2=H (24%)
11b : R1=H, R2=TBS (73%)
TBSCl, imidazole, DMF
room temp., 5h for 11a
50°C, 25h for 11b
12 (80% from 11a)
(95% from 11b)
DIBAL, toluene
-78°C, 15min
13 (97%)
1. CMD, benzene, 50°C, 10h
2. MeMgBr, Et2O, -20°C, 30min
14 (94%)
CMD, benzene
50°C, 14h
15 (98%)
16 , NaH, benzene
100°C, 61h
17 (85%)
DIBAL, CH2Cl2
-78°C, 30min
18 (93%)
1. CMD, benzene, 50°C, 9h
2.
19 , benzene
80°C, 50h
20 (55%)
Me3SiCH2CN, LDA, THF
-78°C, 30min
room temp., 30min
2a : (R1=CN, R2=H) (30%)
2b : (R1=H, R2=CN) (37%)

with lithiotrimethylsilylacetonitrile afforded the tetraene as a mixture of Z-and E-cyanides, **2a** and **2b**, in 30 and 37% yields, respectively. The stereochemical assignment was easily made by the comparison of α-proton signals of the nitrile group in their ^{1}H-NMR spectra : 5.05 ppm for the Z-cyanide **2a** and 5.16 ppm for the E-cyanide.[8] The Z-cyanide **2a** will be utilized for the preparation of calyculins A, C, E, and G while the E-cyanide **2b** will become a precursor for the preparation of calyculins B, D, F, and H.

Thus our methodology involving the C-acylation, the butenolide formation, followed by the stereoselective hydrogenation has well proved to be useful for the preparation of the tetraene fragment of calyculins as its antipodal form. Furthermore, this synthesis will be effectively utilized for the total synthesis of natural calyculins (**1**) starting from (R)-lactic acid.

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References and Notes

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6. The structures of the mono TBS derivatives **11a** and **11b** were assigned by the C5-proton signals in their ^{1}H-NMR spectra ($CDCl_3$): **11a**, 3.37 ppm (1H, triplet, J=4.6 Hz); **11b**, 3.20 ppm (1H, quartet, J=5.3 Hz, changed triplet, J=5.3 Hz, by addition of D_2O).
7. Cf. Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252. CMD (I. C. sample No. 12) was purchased from the I. C. sample office (Cleveland, OH 44101, U. S. A.) and is now available from Chuo Denki Kogyo Co., Ltd. (272 Taguchi, Myokokogen-machi, Nakakubiki-gun, Niigata 949-21, Japan).
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