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Synthesis of the C13-C19 Unit in the Spiroketal Fragment of Calyculins

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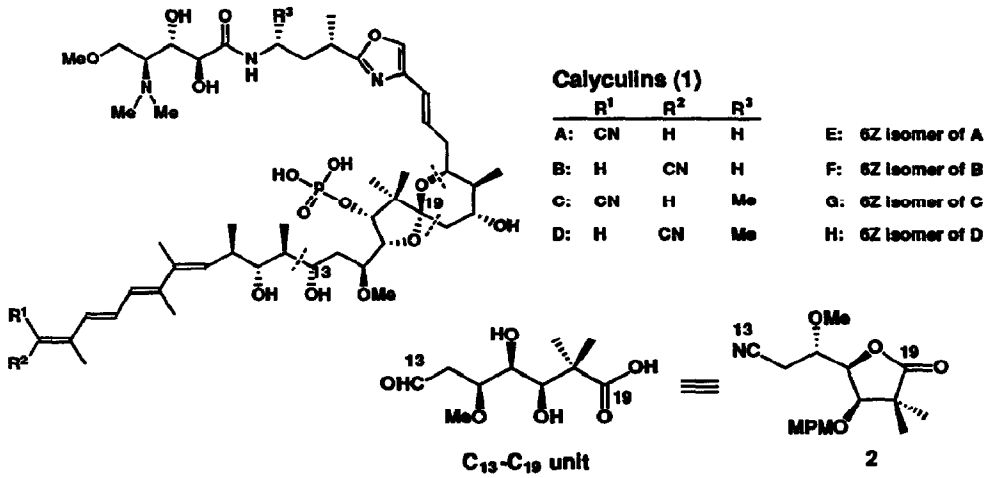
Abstract: Synthesis of the C13-C19 unit 2 of calyculins (**1**) has been accomplished by use of the stereoselective aldol reaction of the aldehyde **10** from diethyl L-tartrate (**3**) with methyl trimethylsilyl dimethylketene acetal followed by the introduction of a cyano group as a C1-unit.

Calyculins isolated from the marine sponge *Discodermia calyx*[1] have interesting biological activities[2] as well as unique structures[1] depicted in **1**. Several groups including ours have attempted the synthesis of **1**,[3] and the antipode of calyculin A has been synthesized.[4] We have already accomplished the synthesis of the C13-C19 unit of calyculins in 16 steps.[3c] We now wish to report an alternative strategy for accessing the C13-C19 unit **2** possessing the natural configuration in shorter steps.[5]



The key features of our synthesis are (1) the formation of the six-membered acetal **8** by oxidative acetalization followed by acidic equilibration and (2) the stereoselective aldol reaction using the chiral borane reagent developed by Kiyooka,[6] as illustrated in Scheme 1. Treatment of diethyl L-tartrate (**3**) with *p*-anisaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) in *N,N*-dimethylformamide (DMF) afforded the acetal **4**.[7] Reductive cleavage of **4** by the known procedures was unexpectedly difficult and gave many products including the ester reduction products. After several trials, sodium cyanoborohydride (6 equiv.) in combination with trimethylsilyl triflate (6 equiv.) in acetonitrile was found to be effective on this cleavage to give the monoprotected tartrate **5**, $[\alpha]^{25}_{D}$ + 67.6° (c 1.01, MeOH), in 83% yield. *O*-Methylation of **5** with methyl iodide and silver oxide in DMF gave the di-protected tartrate **6**, $[\alpha]^{25}_{D}$ + 89.6° (c 1.02, MeOH), which was converted to the diol **7**, $[\alpha]^{25}_{D}$ + 4.24° (c 1, MeOH), by reduction with lithium borohydride. Attempts of selective protection by oxidative acetalization of **7** using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[8] afforded the desired six-membered acetal **8** along with the undesired five-membered acetal **9** in a ratio of 68 : 32. Equilibration of the mixture with TsOH gave the desired product **8**, $[\alpha]^{23}_{D}$ + 42.8° (c 1, $CHCl_3$), in 65% yield from **7** after purification. Swern oxidation of **8** provided the somewhat labile aldehyde **10**, $[\alpha]^{26}_{D}$ +117.4° (c 0.98, $CHCl_3$), which after quick purification on a silica gel column was subjected to stereoselective aldol reactions. Attempt using the lithium enolate of methyl isobutyrate gave the undesired (3*S*)-isomer with complete stereoselectivity. However, the aldol reaction of **10** with commercially available methyl trimethylsilyl dimethylketene acetal in the presence of the chiral borane reagent derived from D-valine in dichloromethane[6] was found to proceed stereoselectively to give the (3*R*)-isomer **11**, $[\alpha]^{23}_{D}$ + 14.2° (c 0.9, $CHCl_3$), in 73% yield. The stereochemistry at the newly created stereogenic center of **11** was determined by its conversion to the lactone **12** through brief acidic treatment. The NMR spectrum of **12** shows the C_3 methine proton at δ 4.10 ppm as a doublet, J=3.6 Hz, together with an N. O. E. of 4% between the C_3 and C_4 protons, indicating the cis relationship between the C_3 and C_4 protons.[9] *O*-Protection of **11** with *p*-methoxybenzyl bromide and sodium hydride in DMF-THF (1:1) gave the acetal **13**, $[\alpha]^{26}_{D}$ -10.8° (c 1.03, $CHCl_3$), which was converted to the lactone **14**, $[\alpha]^{26}_{D}$ + 32.5° (c 1.03, $CHCl_3$), by acidic treatment. Tosylation of **14** followed by cyanation with sodium cyanide in dimethylsulfoxide afforded the desired compound **2**, $[\alpha]^{26}_{D}$ + 11.9° (c 1.05, $CHCl_3$).

It should be worthy of note that the C_{13}-C_{19} unit **2** of calyculins can be efficiently and stereoselectively prepared from the readily available diethyl L-tartrate (**3**) in 11 steps in an overall yield of 13%.

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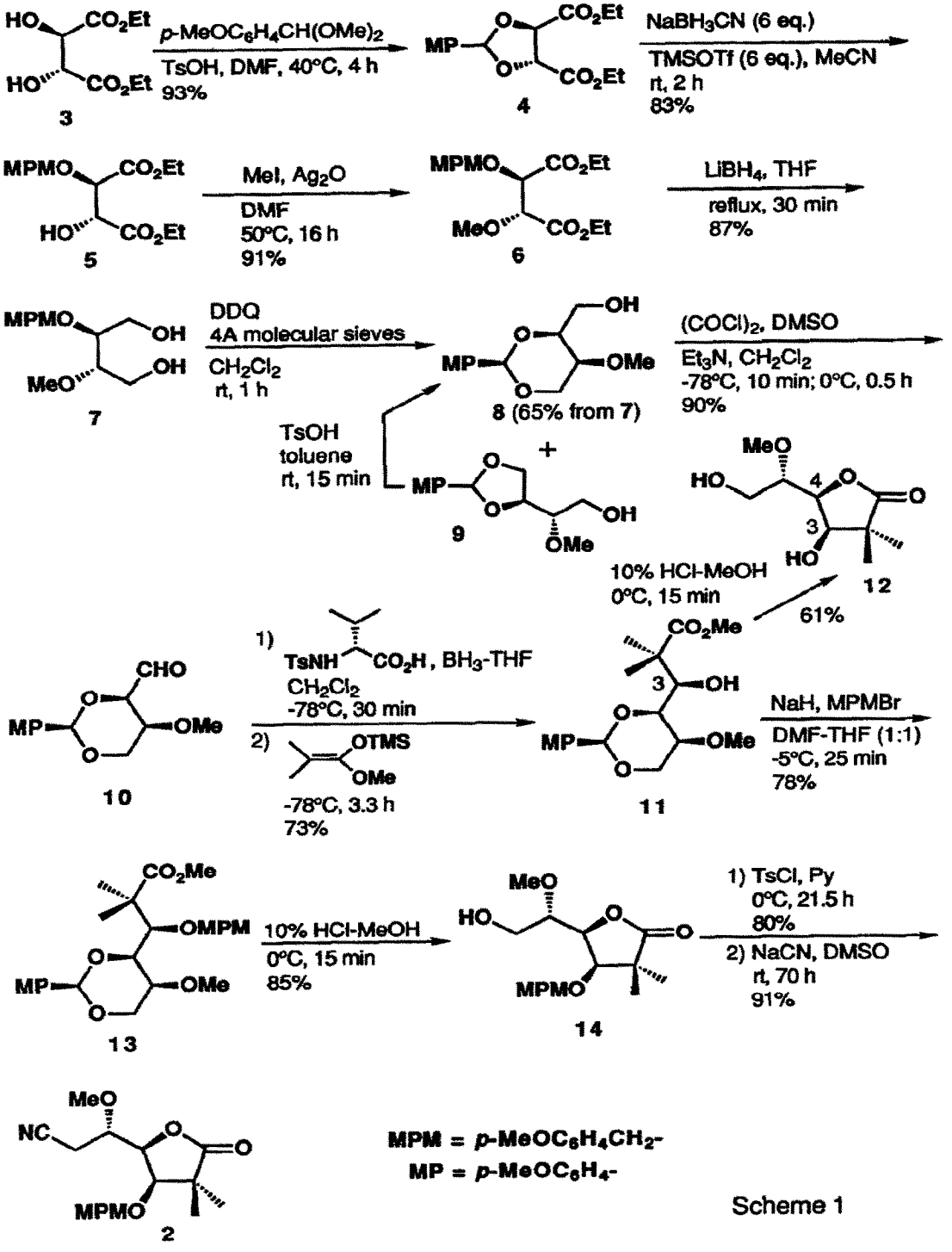
p-MeOC6H4CH(OMe)2
TsOH, DMF, 40°C, 4 h
93%
NaBH3CN (6 eq.)
TMSOTf (6 eq.), MeCN
rt, 2 h
83%
MeI, Ag2O
DMF
50°C, 16 h
91%
LiBH4, THF
reflux, 30 min
87%
DDQ
4A molecular sieves
CH2Cl2
rt, 1 h
TsOH
toluene
rt, 15 min
8 (65% from 7)
(COCl)2, DMSO
Et3N, CH2Cl2
-78°C, 10 min; 0°C, 0.5 h
90%
10% HCl-MeOH
0°C, 15 min
61%
1) TsNH CO2H, BH3-THF
CH2Cl2
-78°C, 30 min
2) OTMS OMe
-78°C, 3.3 h
73%
NaH, MPMBr
DMF-THF (1:1)
-5°C, 25 min
78%
10% HCl-MeOH
0°C, 15 min
85%
1) TsCl, Py
0°C, 21.5 h
80%
2) NaCN, DMSO
rt, 70 h
91%
MPM = p-MeOC6H4CH2-
MP = p-MeOC6H4-

Scheme 1

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