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A Synthesis of the Spiroketal Subunit of (-)-Calyculin A

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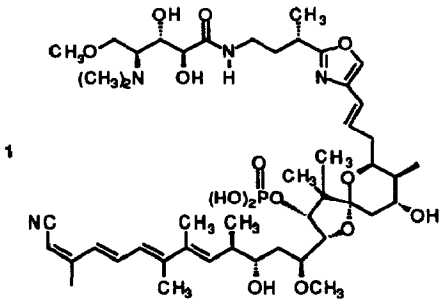
Summary: Using a Ru catalyzed cyclization-addition, a short synthesis of the spiroketal core corresponding to the natural enantiomer of (-)-calyculin A from R-pantolactone emerges.

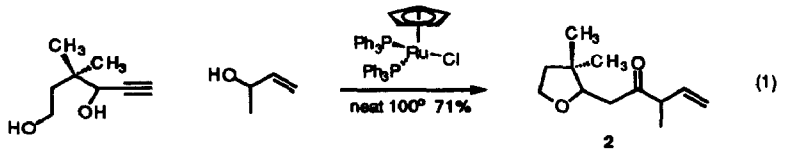
Calyculin A (1), isolated from the marine sponge Discodermia calyx, is a nanomolar inhibitor of two of the four major protein serine/threonine phosphatases which provides an opportunity to probe the cellular processes regulated by these enzymes.[1-3] Among the phenomenological biological consequences observed are its activity



1

in an anti-cell division assay, in cytotoxicity tests against various strains of leukemia cells, and in tumor promotion. While the structure including its relative stereochemistry was established in 1986,[1] its absolute stereochemistry as depicted in 1 was proven only in 1991.[2] Several efforts begun before the reporting of the absolute stereostructure led to approaches to and ultimately a total synthesis of the enantiomer of 1 which had been arbitrarily drawn in the original report.[4,5]

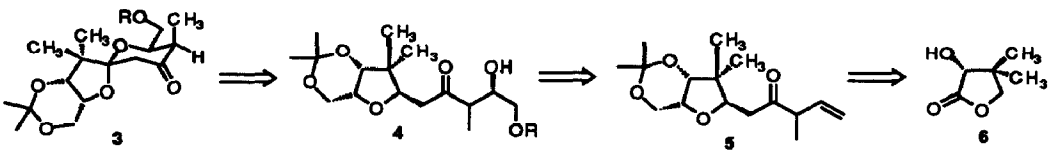
In contemplating a total synthesis, our invention of a simple process for the synthesis of substituted tetrahydrofurans represented by 2 by a ruthenium catalyzed cyclization and addition of an allyl alcohol as in eq



2

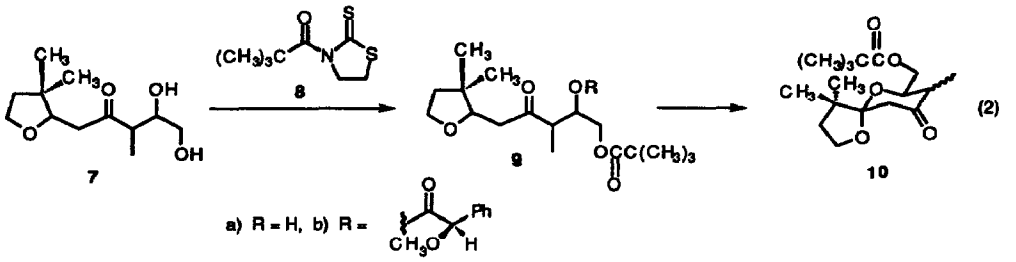
(1)

1[6] focused our initial efforts on the spiroketal core 3. Envisioning the formation of the spiroketal by the oxidative cyclization protocol of Kay[7] and creation of the diol by the asymmetric dihydroxylation procedure of



Sharpless[8] led via 4 to tetrahydrofuran 5 as our proposed intermediate whose assembly should be possible by the reaction of eq 1. The absolute stereochemistry of 5 suggests the readily available R-pantolactone (6) as the chiral building block.

To establish the feasibility of the elaboration of the key tetrahydrofuran intermediate 5 to the desired spiroketal, olefin 2 was subjected to osmium catalyzed dihydroxylation[9] to form diol 7 (eq 2). The propensity for this diol to undergo cyclization and dehydration to a furan led us to cap the primary hydroxyl group under

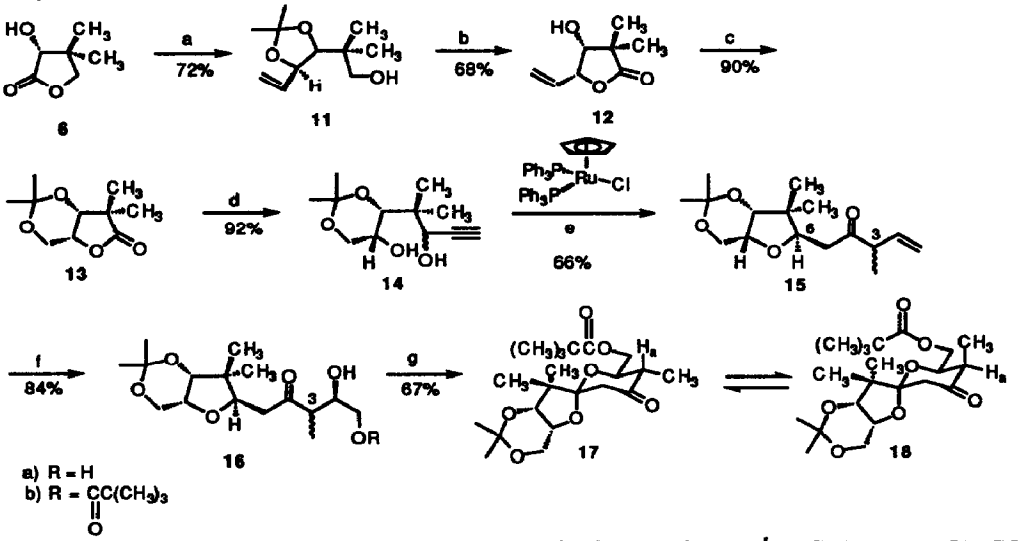


neutral conditions with thiazole 8[10,11] ($PhCH_3$, reflux, 86%). Attempts to effect acylation under acidic or basic conditions failed. Adding monool 9a to a cyclohexane mixture of iodine and mercuric oxide and heating to 100° led to the disappearance of the iodine color after 18 h. The spiroketal 10,[12] isolated in 65% yield, was a 1:1 mixture of two diastereomers epimeric at the methyl group which appeared in the nmr spectrum as two doublets at δ 1.23 and 1.06. The production of only two diastereomers, although the starting diol is a mixture of four, suggests the fact that formation of the spiro center is thermodynamically controlled which leads to the assignment as depicted in 10.

Performing the dihydroxylation of (2) under the conditions of Sharpless using DHQD-PHN[8] and monoprotection as before gave 9a whose ee was assessed by conversion to the O-methylmandelate ester 9b.[13] Since 2 is a mixture of two racemic diastereomers (i.e. four stereoisomers), theoretically 9b can be a mixture of eight stereoisomers if there is no asymmetric induction. Gratifyingly, the nmr spectrum showed signals corresponding to only four--a fact that suggests a high level of asymmetric induction. Since in the real system, we will be employing enantiomerically pure substrates which simplifies the analysis since the number of stereoisomers is reduced, we did not pursue these model studies further.

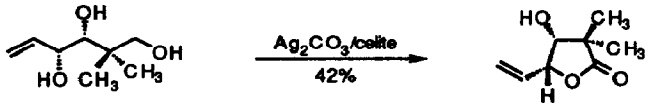
Turning our efforts to the calyculin spiroketal, our substrate for the key ruthenium catalyzed reaction was constructed as illustrated in the Scheme. Reduction of R-pantolactone with 2.5 eq of DIBAL-H (in hexane) in methylene chloride and quenching with methanol led to *in situ* generation of the lactol. After removal of solvent *in vacuo* and direct addition of vinylmagnesium bromide in THF,[14] this reaction was quenched with dilute aqueous hydrochloric acid which allowed easy separation of a granular mixture of aluminum and magnesium salts by filtration.[15] The solution was concentrated, acetone and p-toluenesulfonic acid added to

Scheme. Synthesis of (-)Calyculin Spiroketal



[a]DIBAL-H, CH_2Cl_2, -78°; CH_2=CHMgBr, THF, 0°; CH_3COCH_3, TsOH, rt. [b]PDC, DMF, rt; CF_3CO_2H, rt. [c]O_3, CH_2Cl_2, CH_3OH, -78°, add $NaBH_4$, then CH_3COCH_3, TsOH. [d]DIBAL-H, CH_2Cl_2, -78° then LiC≡CH, THF, -78°. [e]10% Ru catalyst, 20% NH_4PF_6, CH_2=CHCH(OH)CH_3, 100°. [f]DHQD-PHN, $K_3Fe(CN)_6$, K_2CO_3, t-C_4H_9OH, H_2O, 0° then **8**, $PhCH_3$, reflux. [g]HgO, I_2, CCl_4, 70°.

give the protected alcohol **11**[12] in 72% yield after chromatographic purification. GC and nmr (δ 3.82 major, δ 3.73 minor) analysis reveal a 25:1 dr. Formation of lactones **12**[12] and **13**[12] (mp 109-110°) proceeded straightforwardly as outlined in the Scheme. The acetonide protection in the conversion of **6** to **12** can be avoided by the chemoselective oxidation of the triol **19** with the Fetizon reagent[16] (eq 3). However, the higher overall yields using the acetonide led us to favor that route.



(3)

19 **12**

Reduction of the lactone **13** to the lactol followed immediately by addition of lithium acetylide gave the diol **14**[12] as a solid, mp 79°C, whose ^1H and ^{13}C nmr spectra suggested was a single diastereomer. Since the newly created propargylic stereogenic center was destroyed in the ruthenium catalyzed reaction, the assignment of the stereochemistry was not pursued. The crucial ruthenium catalyzed reaction proceeded well to give a 1:1 mixture of two diastereomers **15**,[12] epimeric only at C-3. The exclusive formation of only one diastereomer with respect to the tetrahydrofuran ring represented a higher diastereoselectivity than seen with simpler substrates. The *trans* stereochemistry was assigned by analogy to our earlier work.[6] Since the stereochemistry of C-6 is destroyed in the oxidative cyclization, this point is not important for the calyculin synthesis, but greatly simplifies the characterization of the intermediates.

Asymmetric dihydroxylation gave the diol **16a** which was immediately derivatized to the monopivalate **16b**.[12] Only two diastereomers epimeric at C-3 were generated--a fact which indicates high enantioselectivity

in the dihydroxylation step. Formation of the O-methylmandelate ester of **16a** indicates the dihydroxylation proceeded with >90% diastereoselectivity with the absolute stereochemistry of the major isomer as depicted.[13] While the two epimers could be separated at this point, it was experimentally simpler to do so at the spiroketal stage. Oxidative cyclization proceeded more facilely in carbon tetrachloride than cyclohexane to produce the 1:1 mixture of the epimeric spiroketals **17**[12] and **18**.[12] Nmr spectroscopy clearly indicates the two isomers differ only in the stereochemistry of the secondary methyl group since H_a appears as a dq with the doublet coupling of 10.4 Hz in **17** and 2.4 Hz in **18**. The two isomers can be interconverted by triethylamine to a 3:2 ratio of **17:18** and thereby permit complete conversion to the desired epimer **18**. This route provides enantiomerically pure calyculin A spiroketal corresponding to the correct configuration of the natural product from R-pantolactone in 12 steps (7 stages) and 15% overall yield.

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