Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6051-6052, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01295-4

CALYCULIN SYNTHETIC STUDIES. 4. REMARKABLE REVERSAL OF DIASTEREOSELECTIVITY IN PAYNE EPOXIDATION OF VINYL SPIROKETAL INTERMEDIATES

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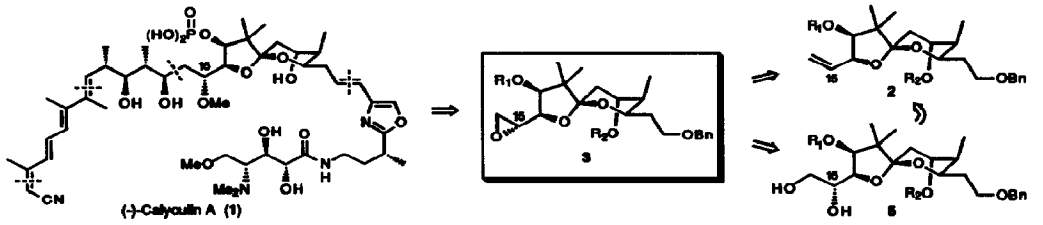
Abstract: Differential protection of two secondary hydroxyl groups led to a dramatic reversal of diastereofacial selectivity in Payne epoxidation of vinyl spiroketals **2a-g**, key building blocks in a proposed total synthesis of calyculins A-H.

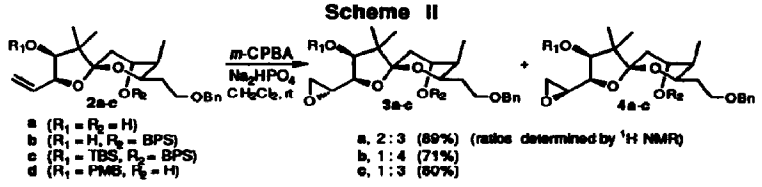
In connection with our program directed toward the total synthesis of the calyculins (A-H; e.g., **1**),[1,2] architecturally novel metabolites of the Japanese sponge *Discodermia calyx*,[3] we required a method for stereocontrolled generation of a C(14,15) α-epoxide **3** (Scheme I). Herein we describe epoxidation and dihydroxylation reactions of vinyl spiroketals **2a-g**.[1a] Variations of the oxidant and the substrate protecting groups efficiently furnished both C(15) epimers and revealed a dramatic reversal of diastereoselectivity in Payne epoxidations.

Scheme I



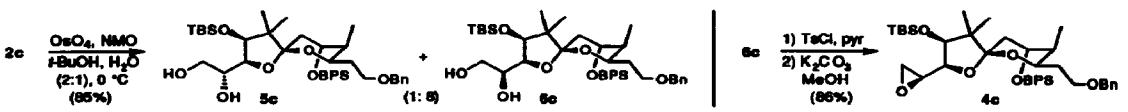
Although our analysis of the vinyl spiroketal structures did not yield clear-cut predictions of oxidation stereochemistry,[4] Ōmura and co-workers observed a modest preference (ca. 1.8:1) for the isomers we required in *m*-CPBA epoxidation of two 2-alkenyl tetrahydrofuran derivatives related to **2**.[5] Unfortunately, treatment of vinyl spiroketals **2a-c** with *m*-CPBA furnished predominantly the undesired β epoxides **4a-c**,[6] whereas **2d** gave a complex mixture (Scheme II).

Scheme II



We next explored the catalytic osmium tetroxide dihydroxylation of **2c**. Osmylation and peracid epoxidation often afford complementary stereoselectivities,[7] but dihydroxylation of **2c** provided the α and β diols **5c** and **6c**[6] in a 1:8 ratio (85% yield; Scheme III). The major isomer was readily converted to the β epoxide **4c**.[6]

Scheme III

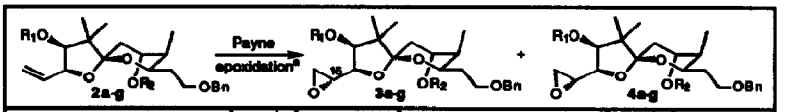


In an effort to exploit reagent control of the C(15) configuration, we turned to the Sharpless asymmetric dihydroxylation (AD) process.[8] Osmylation of **2** with an appropriate scalemic ligand was expected to deliver the requisite

absolute stereochemistry in diol **5**, but we observed instead that pseudoenantiomeric reagents generally gave *identical* diastereomer mixtures in which the undesired epimers predominated. These surprising results will be described elsewhere.[9]

Finally, we investigated the stereochemistry of Payne epoxidation[10] of **2**. Despite the structural similarities between peracids and peroxybenzimidic acid, the latter the presumed[10a,b] Payne reactive species, Payne and peracid epoxidations have previously expressed opposite diastereofacial preferences.[10b,c] We were delighted to find that Payne epoxidation of vinyl spiroketal **2d** furnished the required 15α epoxide **3d** in 81% yield after chromatographic separation of the 9.5:1 epimer mixture. Moreover, differential protection of the two secondary hydroxyl groups led to a dramatic reversal of diastereoselectivity (Table I). The results suggest an unusually complex interplay of conformational effects and steric and hydrogen bonding interactions.

Table 1



Vinyl spiroketal	3:4[b]	Yield (%)[c]	Vinyl spiroketal	3:4[b]	Yield (%)[c]
2a $R_1 = R_2 = H$	3:1	82	**2e** R_1 = Ac, R_2 = H	4:1	85
2b R_1 = H, R_2 = BPS	1:18	86	**2f** R_1 = TBS, R_2 = H	8.6:1	80
2c R_1 = TBS, R_2 = BPS	--	N.R.[d]	**2g** R_1 = Ac, R_2 = BPS	--	N.R.[d]
2d R_1 = PMB, R_2 = H	9.5:1	89			

[a] 30% H_2O_2, PhCN, $KHCO_3$, MeOH; 0 °C, 40 h. [b] Determined by ^1H NMR. [c] Combined isolated yield. [d] No reaction occurred at 0 °C or at room temperature.

Further progress toward the total synthesis of the calyculins will be reported in due course.

Acknowledgment. Financial support was provided by the National Institutes of Health (National Cancer Institute) through grant 19033. We thank Dr. George T. Furst, Dr. Patrick J. Carroll and Mr. John Dykins for assistance with NMR, X-ray and mass spectral analyses, respectively.

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(*Received in USA* 13 *June* 1994; *accepted* 30 *June* 1994)