Tetrahedron Letters,Vol.30,No.51,pp 7157-7160,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

An Unusual Stereochemical Directing Effect of Propargylic Oxygen Substituents on an Intramolecular Diels-Alder Reaction

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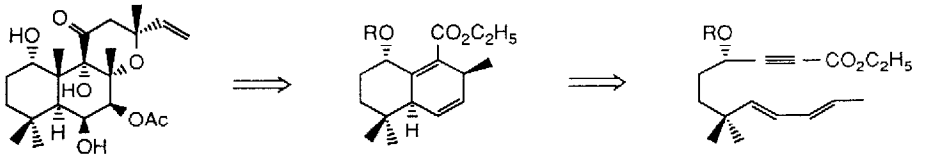
Summary. Varying the substituent on the oxygen of a propargylic alcohol affects the stereochemical course of an intramolecular Diels-Alder reaction of a diene-yne.

The powerful effects of forskolin (1) on the second messenger regulatory system involving the cellular concentration of c-AMP controlled by adenylate cyclase appears to lead to a variety of therapeutically useful physiological effects.[1] Understanding the structural basis for these biological effects combined with the structural challenge of the densely functionalized decalin ring bearing a fused 4-pyranone ring make this system an exciting and

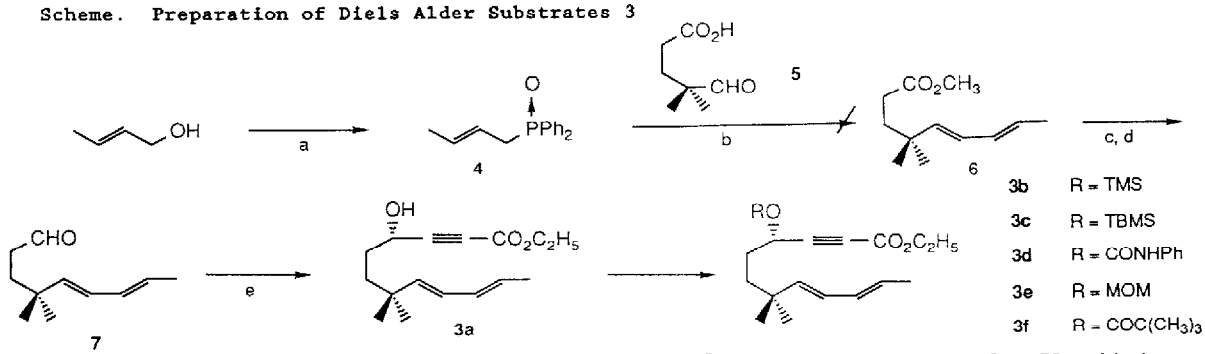


1 2 3

important synthetic target.[2,3] Our interest in the synthetic challenge derived from the opportunity to explore stereocontrolled ways to construct the 4-pyranone, and to provide a scalemic synthesis of the decalin portion. Considering the elaboration of the hexalin 2 to form the appropriately functionalized decalin, the entire stereochemistry of forskolin would then flow from the propargylic alcohol stereocenter of the acyclic precursor 3, whose absolute stereochemistry can be readily controlled[4]. In this paper, we wish to record an unusual dependence of the diastereoselectivity of the intramolecular Diels-Alder reaction on the choice of alcohol substituent - a fact that may reveal unusual stereoelectronic effects in the reactions of the acetylenes.

For the preparation of the E,E-diene, we required the pure E phosphine oxide 4[6] which was readily prepared in a two pot procedure from E-crotyl alcohol, the latter best obtained by reduction of E-crotonaldehyde to optimize obtention of the E-geometrical isomer (see Scheme). Practical conditions for obtaining the desired E, E-diene 6 involve reacting the lithium derivative of 4 with the lithium salt of the aldehydic acid 5[7] formed upon treating the latter with 1 eq of n-butyllithium which gave a 7:1 E, E(6[8]) to E,Z mixture of dienes.

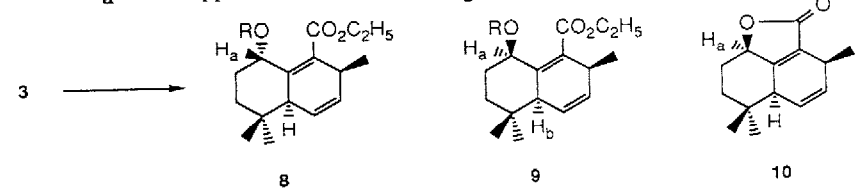
Scheme. Preparation of Diels Alder Substrates 3



a) i. n-C_4H_9Li, THF, 0° then TsCl, rt then Ph_2PLi, 0°; ii. 7% aq. H_2O_2, $CHCl_3$, 71%. b) i. n-C_4H_9Li, THF, -78°; ii. CH_2N_2, ether, 73%. c) LAH, THF, 0° to rt, 76%. d) DMSO, $(COCl)_2$, CH_2Cl_2, -60°, $(C_2H_5)_3N$, -60° to 0°, 95%. e) Li -C≡C-$CO_2C_2H_5$, THF, -78°, 94%. f) **3b**: BSA, DMF, rt, 78%; **3c** : TBDMS-Cl, imidazole, DMAP, DMF, 0° to rt, 94%; **3d** : PhNCO, C_5H_5N, CH_2Cl_2, rt, 62%; **3e** : CH_3OCH_2Cl, $(C_2H_5)_2NH$, CH_2Cl_2, 0° to rt, 82%; **3f** : t-C_4H_9COCl, 1-methylimidazole, DMAP, CH_2Cl_2, 0° to rt, 77%.

Whereas, reduction of ester **6** proceeds straightforwardly, oxidation of the primary alcohol to the aldehyde required a slight modification of the Moffatt - Swern oxidation wherein oxalyl chloride is added to a mixture of the alcohol and DMSO in methylene chloride followed by addition of the base. The alcohol **3a** was derivatized in the normal fashion to give the substrates **3b - 3f**.

The cyclizations were performed either thermally (**3b**) or in the presence of ethylaluminum dichloride (**3b**) or diethylaluminum chloride (**3c - 3f**) to give the cycloadducts **8**,[8] **9**,[8] and/or **10**.[8] The products are readily distinguishable by ^1H NMR spectroscopy wherein the signal for H_a in **8** appears as a broad singlet indicating its equatorial nature; whereas



8 **9** **10**

a) R=H b) TMS c) R=TBDMS d) R=CONHPh e) R=MOM f) R=$COC(CH_3)_3$

the signal for H_a in **9** appears either as a triplet (J=7.2 Hz) or as a ddd (J=11-12, 5-6, 1-3 Hz) demonstrating its axial nature. Further proof for structure **9** derives from the 8-10% NOE enhancement seen between H_a and H_b and the cyclization to the lactone **10** which also exhibits a triplet (δ 4.74, J=8.1 Hz) for H_a indicating its axial nature.[9]

All attempts to cyclize the free alcohol **3a** either thermally or under conditions of Lewis acid catalysis failed. On the other hand, the trimethylsilyl ether **3b** underwent thermal isomerization ($PhCH_3$, 170°) to give a 75% yield of **8b**. Strikingly, utilizing 1.1 eq. of ethylaluminum dichloride gave the lactone **10** exclusively, albeit in only 30% yield. The lower yield in this case derives from the lability of the trimethylsilyl group under the conditions of the Lewis acid catalyzed reaction. To the extent that desilylation occurs, decomposition ensues. In fact, cyclization of the more robust t-butyldimethylsilyl ether

leads to an 80% yield of cycloadduct 9c, the stereoisomer which is the precursor of the lactone.

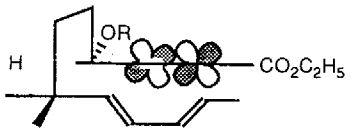
Table. Diastereofacial Selectivity of the Intramolecular Diels-Alder Reaction[a]

Entry	Substrate	Eq. Lewis Acid[b]	Temp.	Ratio 8 : 9 : 10	Ratio 8 : 9 + 10	Yield
1	3b	1.1	25°	only 10		30%
2	3c	1.1	25°	only 9c		80%
3	3d	3	25°	1:0.83:0.17	1:1	60%
4	3d	3	0°	4:1.0:0.13	1:0.38	55%
5	3e	2	25°	4:1.0: -	4:1	50%
6	3e	2	0°	6:1.0: -	6:1	50%
7	3f	2.5	rt	only 8f		84%
8	3b	0	170°	only 8b		75%

a) All reactions were performed in toluene. b) Diethylaluminum chloride was employed in all cases except entry 1 wherein ethylaluminum dichloride was employed.

The Table summarizes the Lewis acid catalyzed Diels-Alder reactions. In each, the number of equivalents of Lewis acid corresponded to that required for cyclization. *Under similar conditions, completely opposite diastereofacial selectivity (cf. entries 2 and 7 or 8) is observed simply as a function of the oxygen substituent!* A possible explanation invokes steric effects. MM-2 calculations reveal that the relative stability of 8 and 9 depends upon the substituent. For R=H, the equatorial oxygen isomer 9 is the more stable, but if R = t-C_4H_9, the $A_{1,3}$ strain dominates, and the axial oxygen isomer 8 is now slightly favored. Considering the transition state (ts) for the intramolecular Diels-Alder reaction as product-like, we can consider the relative stability of the forming products as a function of the substituent to determine the reaction course. Because of the lower Lewis basicity of the silyl ethers 3b and 3c, the Lewis acid coordinates only to the ester. Apparently, the $A_{1,3}$ strain of 9b and 9c is less important than the 1,3-diaxial interactions of 8b and 8c, and only the equatorial oxygen product is observed. On the other hand, all other oxygen substituents required at least 2 eq of Lewis acid - a fact that suggests coordination with both the oxygen substituent and the ester. The resulting $A_{1,3}$- strain developing in the ts for the bis-coordinated system favoring formation of 8 begins to dominate over the 1,3-diaxial interactions as suggested by the MM-2 calculations. This effect is optimized with the sterically most bulky oxygen substituent, pivalate, and only the axial oxygen product 8f is observed.

An alternative intriguing explanation considers a stereoelectronic effect. In the two diastereomeric ts, the propargylic substituent can be seen to be perpendicular to the remaining π system in 11 (leading to 8) but parallel in 12 (leading to 9 or 10)[10]. Coordination of a Lewis acid with the oxygen substituent may disfavor the ts proceeding via 11 since any contact with the oxygent substituent is being lost, thereby favoring 12. While it is tempting to favor the simple steric argument, the possibility that such stereo-



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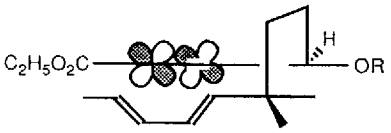

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electronic effects may be important in the reactions of acetylenes is intriguing.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We thank Mr. A. Trost for performing some of the MM-2 calculations.

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(Received in USA 27 June 1989)