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Intramolecular Alder Ene Reaction of Activated 1,6-Dienes : Stereochemical Control over Three Contiguous Stereogenic Centres

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Abstract : An intramolecular ene approach to stereocontrol over contiguous stereogenic centres is described, where three centres can be created with very high level of both diastereofacial selectivity and diastereoselectivity by the influence of an oxygen substituent as a stereodirecting resident group in the ene component.

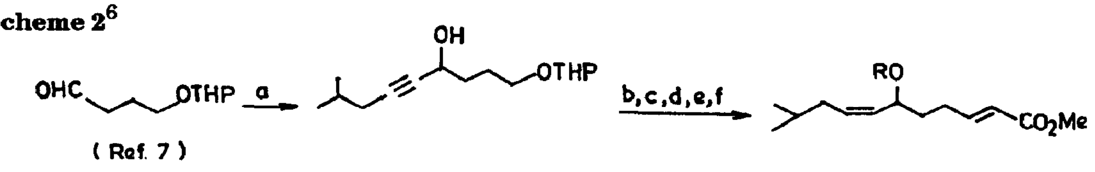
The intramolecular ene reaction has recently received considerable attention[1] and offers a valuable method for carbo- and heterocyclization. The stereochemistry about the forming carbon-carbon bond is usually *cis* for five-membered rings. The relationship between the stereochemistries of substituents on the tether and the stereochemistry of carbon-carbon bond formation is not, however, as easily predicted.[2] As part of our continuing program to explore the potential of intramolecular ene reactions for organic synthesis,[3] we were interested to study the topological influence (C-4) over developing (C-3, C-7) stereogenic centres in the ene cyclization step (Scheme 1).

Scheme 1

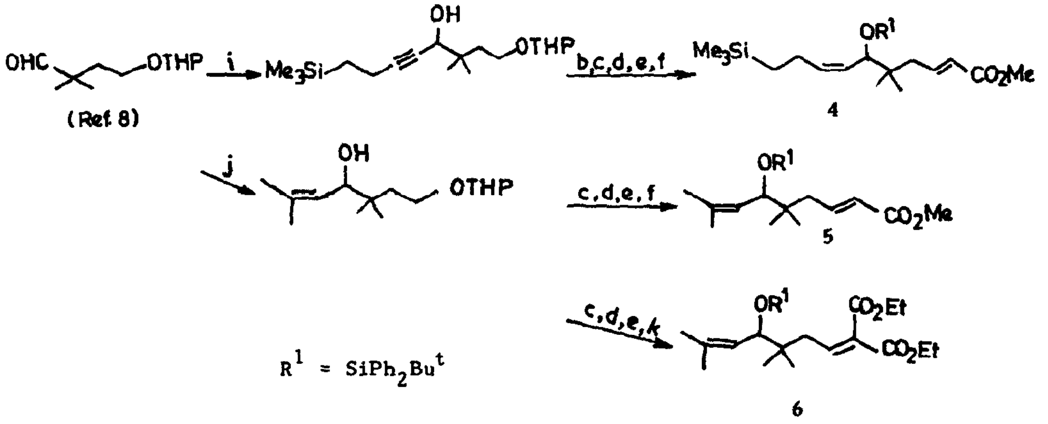
Although a few reports have dealt with this issue (X = CH_3; Y = O/CH_2),[1d] the influence of an oxygen substituent(X = OR) as a stereodirecting resident group in the ene compartment has not been systematically investigated.[4] Prompted by the occurrence of hydroxyl-bearing chiral centres in cyclopentanoid natural products,[5] we have now studied this facet of 5-(3,4) ene cyclizations[1d] using six 1,6-dienes, **1-6**, and in this letter we wish to report the preliminary results of our investigation.

The parent dienes, **1-6**, with different substituents on the ene, the tether and the enophile were prepared following standard synthetic techniques as summarized in Scheme 2.[6]

Scheme 2[6]

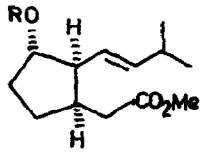


g{1 : R = $SiPh_2Bu^t$
2 : R = H
h{3 : R = $SiMe_2Bu^t$

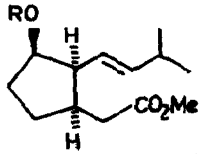


(a) $LiC{\equiv}CCH_2CH(CH_3)_2$/THF-HMPA, -78°, 80% (ref.11); (b) i-BuMgBr/Cp_2TiCl_2 (cat.), 68% (ref.12); (c) t-$BuPh_2SiCl$/Im/DMF, 92%; (d) PPTS, ethanol, 97%; (e) DMSO/$(COCl)_2$, 90%; (f) $(MeO)_2P(O)CH(Li)CO_2Me$, followed by purification by prep. tlc, 80% (ref.13); (g) 3% HCl-MeOH, 59%; (h) t-$BuMe_2SiCl$/Im/DMF, 95%; (i) $LiC{\equiv}CCH_2CH_2SiMe_3$/THF-HMPA, -78°, 87% (ref.14); (j) $Me_2C{=}CHMgBr$, 52%; (k) $CH_2(CO_2Et)_2$/piperidinium acetate, 83%.

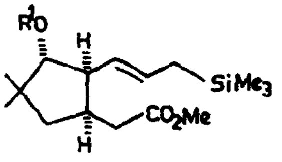
The thermolytic cyclizations of **1**, **3**, **4** and **5** were carried out in toluene (5% solution) in a sealed tube under an atmosphere of argon. Attempts to cyclize the free alcohol **2** under this condition failed as it underwent extensive decomposition. The ene reaction of **6** was effected at ambient temperature in CH_2Cl_2 in the presence of a Lewis acid($ZnBr_2$). The product ratios (Table 1[6]) were determined by high-field NMR and capillary GC analysis.[15]



7, R = $SiMe_2Bu^t$
9, R = $SiPh_2Bu^t$



8, R = $SiMe_2Bu^t$
10, R = $SiPh_2Bu^t$



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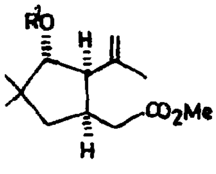

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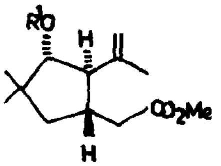

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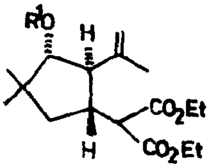

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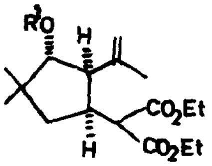

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R^1 = $SiPh_2Bu^t$

Table 1 reveals the following significant features of the present ene reaction. In runs 1 and 2, diastereoselectivity is uniformly high, but the diastereofacial selectivity increases with increasing steric bulk of the silyl[17] substituent on oxygen. The most astonishing result is, however, observed in run 3 where the 1,6-diene **4** carrying a strategically located TMS group gives the cyclopentanoid allylsilane **11** in very high yield with nearly 100% diastereoselectivity and 100% diastereofacial selectivity! While **11** should serve as a key intermediate[3e] for coriolin,[18] **9/10** may be tailored into oreodaphnenol[19] via intramolecular keto-carbenoid addition across the *E*-double bond. In runs 4 and 5, while diastereofacial selectivity is very high, diastereoselectivity actually increases in the Lewis acid catalyzed reaction in accordance with previous observations.[3a,b,20,21]

Table 1[6,15]: Stereochemical Control over Three Contiguous Stereogenic Centres

Run [a,b]	Educt	Temp./time	Products/(ratio [c])		Combined Yield [d]	Diastereoselectivity / diastereofacial selectivity[e]
1	**3**	235°C/40h	**7/8**	(79:21)	83%	~100% *cis*/79%*trans*
2	**1**	235°C/40h	**9/10**	(88:12)	97%	~100% *cis*/88% *trans*
3	**4**	235°C/18h	**11**		96%	~100%*cis*/~100% *trans*
4	**5**	235°C/40h	**12/13**	(88:12)	86%	88% *cis*/100% *trans*
5	**6**	r.t./2h	**14/15**	(96:4)	90%	96% *trans*/100% *trans*

[a] In runs 1-4, a 5% solution of the diene in toluene was heated in a sealed corning tube under argon. In run 5, a 0.5M solution of the diene in CH_2Cl_2 was exposed to $ZnBr_2$ (anhyd.). [b] The GC traces in these runs are as follows : run 1 (1.8:77.7:20.5); run 2 (1.09:81.4:5.57:11.9); Run 3 (96.4:1.9:0.6:1.1); run 4 (11.9:87.5:0.6); run 5 (95.6:4.4). [c] Trace diastereomers were not properly characterized. [d] Isolated after chromatography. [e] Trace diastereomers were ignored.

A culmination of this type of 5-(3,4) ene cyclization methodology is its ideal application to the diastereoface selective and diastereoselective synthesis of (±)-cucurbic acid methyl ester as described in the accompanying paper.

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