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Stereospecific Synthesis of (*Z,E*)-Dienes. An Experimental Verification of Houk's Group Theoretical Predictions for Nitrogen Substituents.

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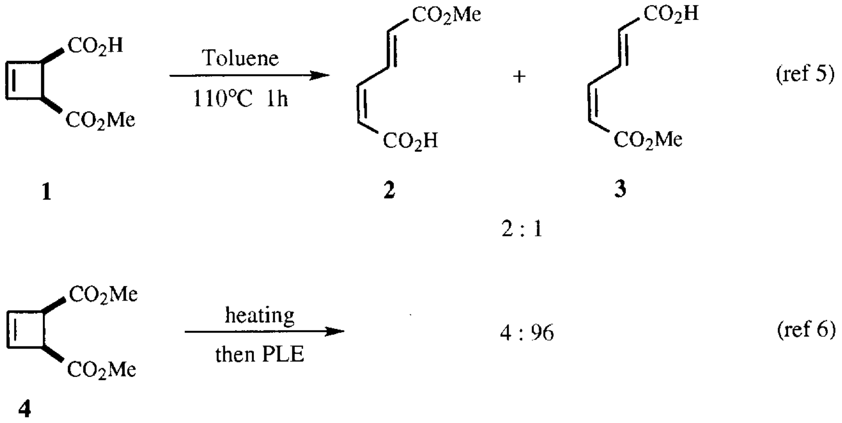
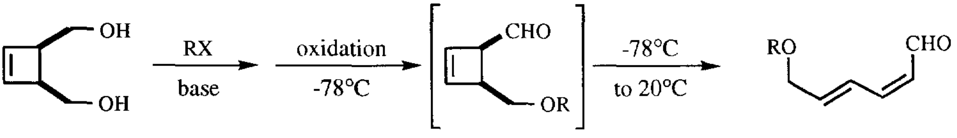
Abstract : Heating of several *cis*-1,2-disubstituted 3-cyclobutenes exclusively led to (*Z,E*)-dienes corresponding to the outward conrotation for nitrogen substituents. Copyright © 1996 Elsevier Science Ltd

Stereocontrolled preparation of substituted conjugated dienes or polyenes can be achieved by various methods.[1] One of them involves, as the starting materials, cyclobutene derivatives, which are available by *syn,syn* [2+2] photochemical cycloaddition. Orbital symmetry selection rules[2] predict that (*Z,E*)-dienes, for instance, might be produced by the thermal electrocyclic ring opening of *cis*-1,2-disubstituted 3-cyclobutenes or by the photochemical opening of *trans*-compounds. The experimental results are consistent with these rules for thermal reactions.[3] In the case of irradiation, the reaction proceeds nonstereospecifically and it works together with cycloreversion.[4] Although the thermal ring opening leads to an excellent stereochemical control, a possible limitation on the synthetic point of view, from unsymmetrical *cis*-1,2-disubstituted 3-cyclobutenes, is the formation of two isomeric (*Z,E*)-dienes. For instance hemiester **1** gives both opening products **2** and **3** in poor selectivity.[5] We have shown[6] that a way to obtain one of both isomers, predominantly, is *via* the thermal opening of a symmetrical compound **4** followed by a stereoselective enzymatic reaction (Scheme 1).



Scheme 1

However unsymmetrical compounds do not always yield mixtures, and theoretical as well as experimental studies are in agreement with a stereochemical result strongly dependent on the electronic effects of the allylic substituents. The π-donors mainly or exclusively lead to outward rotation and π-acceptors, to inward rotation.[7] Obviously, when both substituents have complementary preferences in the conrotatory mode, the thermal ring opening may give one of the both (*Z*,*E*)-dienes in high isomeric purity. Moreover this complementarity highly facilitates the ring opening that then occurs at low temperature. Such an example is given in scheme 2.[8]



5 **6** **7**

R = 4-$MeOC_6H_4CH_2$

isomeric purity > 97%
(ref 8)

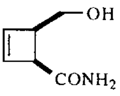
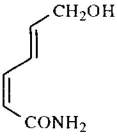
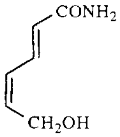
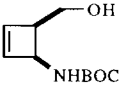
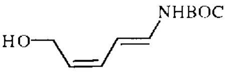
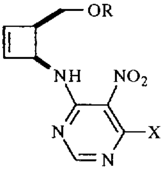
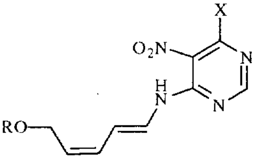
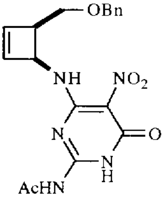
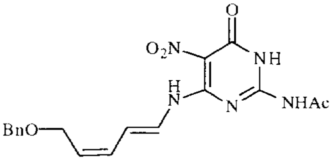
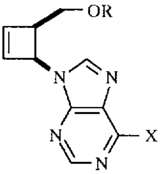
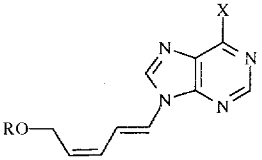
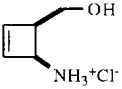
Scheme 2

Theoretical predictions from Houk's group, published for the first time several years ago and confirmed recently,[7] state that the NH_2 group should be a substituent with one of the strongest outward preference. Observation of this preference for nitrogen substituents is very rare in the literature due to the small number of such compounds that have been synthesized. However it was pointed out in the course of heating, in the presence of ammonia, of a cyclobutene compound substituted, at the allylic position, by a 9-(6-chloropurine) group,[9] and of heating of*cis*-fused 3-(dialkylamino)cyclobutenes.[10]

In the course of our syntheses of cyclobutene nucleoside analogues[11] *e.g.* **12b**, we encountered difficulties due to the ring opening of the intermediates; however we could obtain satisfactory overall yields by using mild experimental conditions. It seemed interesting to submit several intermediates or products to heating to examine which isomers were predominant in the electrocyclic reactions. Each experiment was run at about 10 mg scale and heating was pursued until disapearance of the starting material. ^1H NMR spectra then only showed signals corresponding to dienes, except when starting from **13** (Table 1). We were pleased to observe that nitrogen substituents led to outward rotation, exclusively, in complete agreement with Houk's group predictions. In some cases a subsequent thermal isomerization into (E,E)-products occured. On the other hand isomerization of amido-alcohol **8** also led to the expected result, as **14a** was obtained predominantly.

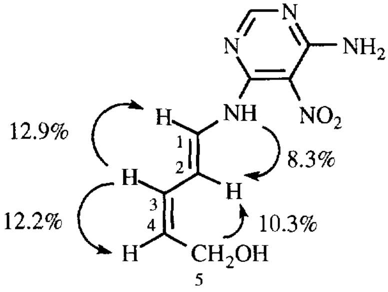
The stereochemical assignments for products **14** to **18** were based on ^1H NMR results. Coupling constants were higher for the *trans*-relationship than for the *cis*-ones, however the differences were not very high. Therefore we also measured NOE enhancements (*e.g.* **10c**, Scheme 3).

We also submitted several samples to heating at a lower temperature than for the the total conversion into dienes in order to obtain informations on relative isomerization rates (Table 1). We thus observed that isomerization was quicker in the case of **9**, than when nitrogen was conjugated with an electron poor aromatic heterocycle (**10a**, **10b**) or belonged to an aromatic cycle (**12a**, **12b**). Therefore diminution of the π-donor effect of the subtituent led to a slowing down of isomerization.

	Isomerization product (experimental conditions)	% of Dienes after 1h at 60°C [e]
 **8**	 +  **14a** 94:6 **14b**	2
 **9**	 exclusively [a] **15**	50
 **10a** R = Bn, X = Cl **10b** R = Bn, X = NH_2 **10c** R = H, X = NH_2	 exclusively **16a** (b) **16b** (b) **16c** (c)	13 20 —
 **11**	 exclusively **17** (b)	—
 **12a** R = Bn, X = Cl **12b** R = H, X = NH_2	 exclusively [a] **18a** (b) **18b** (c)	2 1
 **13**	Degradation products (d)	0

a compounds **15** and **18a** progressively isomerized into (*E,E*)-products on standing ; b Toluene, reflux, 0.5h (**9**), 1h (**10a**, **10b**, **11**), 1.5h (**8**, **12a**) ; c DMSO-d6, 110°C, 1h ; d toluene, 100°C, 1h ; e Solvent $CDCl_3$ (**9**, **10a**, **10b**, **12a**) or DMSO-d6 (**8**, **12b**)

Table 1



$J_{H\text{-}1/H\text{-}2} = 13.8$ Hz

$J_{H\text{-}3/H\text{-}4} = 10.8$ Hz

Selected NOE Enhancements

Scheme 3

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