183. A New Stereoselective Approach to Substituted Pyrrolidines by Intramolecular Ene-Reactions[1])

Preliminary Communication[2])

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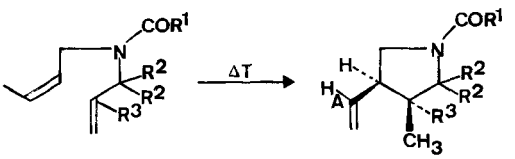
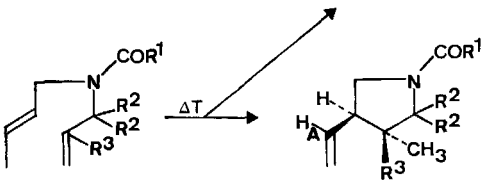
Zusammenfassung. In der vorliegenden Mitteilung wird erstmals die Stereochemie intramolekularer En-Reaktionen in Beziehung zur Geometrie der En-Komponente systematisch beschrieben sowie ein neuer, präparativ ergiebiger Weg zu substituierten Pyrrolidinen aufgezeigt. Die N-(*cis*-Crotyl)-N-allylamide **1** werden beim Erhitzen ausschliesslich zu den Pyrrolidinen **2** isomerisiert. Unter identischen Bedingungen entstehen aus den N-(*trans*-Crotyl)-N-allylamiden **3** die gleichen Stereoisomeren **2** neben geringeren Mengen der epimeren Nebenprodukte **4**. Durch die Umsetzungen **5** → **6**, **7** → **8** + **9**, **10** → **11** und **12** → **13** wird die thermische Überführung cyclischer Olefine in polycyclische Pyrrolidine unter sterischer Kontrolle mehrerer Chiralitätszentren illustriert. Während die Reaktion **14** → **15** schärfere Bedingungen erfordert, zeigen die Isomerisierungen **16** → **17** und **18** → **19** die glatte Beteiligung von C,C-Dreifachbindungen an intramolekularen En-Reaktionen bei weniger hohen Temperaturen.

As part of a program directed towards stereoselective syntheses of five-membered ring systems, intramolecular ene-reactions[3]) have been examined. In particular, it seemed desirable to study the possible influence of the ene-geometry on the *endo/exo*-ratio of such transformations[4]).



1 **2**



3 **4**

[1]) Presented in part at the International Symposium: «Neue Methoden der Organischen Synthese», Basle, Switzerland, May 11, 1973.

[2]) The content of this communication will appear as part of a full paper in this journal.

[3]) For general information on ene-reactions see the review of *Hoffmann* [1]. Recently an intramolecular example has been described by *Kelly* [2].

[4]) The *exo vs. endo* stereochemistry of an *intermolecular* ene-synthesis has been studied by *Berson et al.* [3].

Table 1. *Thermolysis of the N-(*cis- *and* trans-*crotyl)-N-allylamides* **1** *and* **3**

Starting Diene	R^1	R^2	R^3	Reaction Conditions[5])	Total yield of Pyrrolidines[6])	% **2**[7])	% **4**[7])
1a[8])	CH_3	H	H	280°/7 h	88%	100.0 **2a**	–
3a[9])	CH_3	H	H	280°/7 h	80%	89.0 **2a**	11.0 **4a**
1b[10])	CH_3	H	C_6H_5	230°/42 h	55%	100.0 **2b**	–
3b[10])	CH_3	H	C_6H_5	230°/42 h	55%	84.5 **2b**	15.5 **4b**
1c[11])	OCH_3	CH_3	H	230°/63 h	82%	99.8 **2c**	0.2 **4c**
3c[12])	OCH_3	CH_3	H	230°/63 h	90%	74.0 **2c**	26.0 **4c**

[5]) Chromatographically purified dienes in toluene (5%) were heated in sealed ampoules under nitrogen.

[6]) Isolated after chromatography on silica gel.

[7]) Starting materials and products were analyzed (and the latter separated) by GC. The ratio **2**:**4** cited in Table 1 is corrected for the stereochemical purity of the starting materials.

[8]) Prepared by acetylation of *cis*-crotylamine [4], reaction of the acetamide with 1 equiv. sodium hydride in dry hexamethylphosphoramide and alkylation of the resulting sodium salt with excess allyl bromide.

[9]) Prepared by alkylation of the sodium salt of allylacetamide with *trans*-crotyl bromide as described above.

[10]) Prepared by alkylation of the sodium salt of corresponding crotylacetamide with α-bromomethylstyrene [5].

[11]) Obtained from 2.2-dimethyl-but-3-enoic acid [6] by *Curtius* degradation, alkylation of the resulting methyl α,α-dimethylallylcarbamate with 1-bromo-2-butyne [7] and partial hydrogenation of the acetylene with *Lindlar* catalyst in benzene.

[12]) Prepared by alkylation of the sodium salt of methyl α,α-dimethylallylcarbamate with *trans*-crotyl bromide.

As indicated in Table 1 the *cis*-crotylamides **1**, on thermolysis, cyclized stereospecifically to the *cis*-substituted pyrrolidines **2**, which were isolated in high yields. Under identical conditions the *trans*-crotylamides **3** isomerized smoothly at comparable rates, to give preferably the same stereoisomers **2**, together with minor amounts of the *trans*-substituted pyrrolidines **4**.

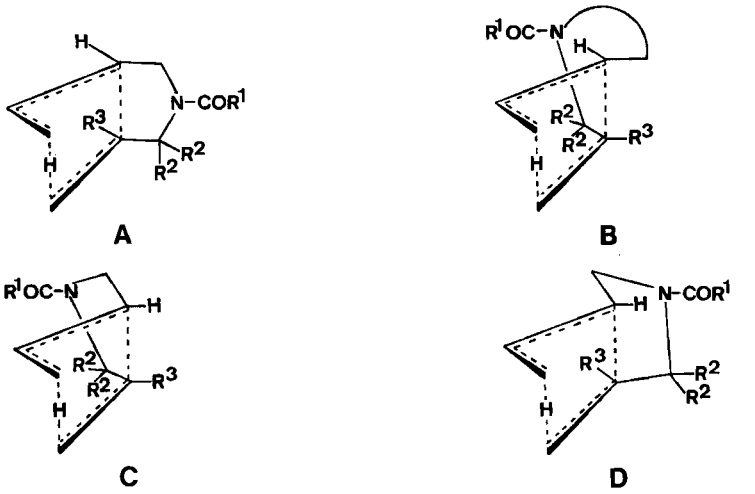
The *cis*-configuration of the pyrrolidine **2a** was established by *T. J. Petcher* [8] *via* X-ray analysis of the corresponding N-benzyl-N-methyl-pyrrolidinium iodide, whereas the stereochemistry of the products **2b**, **4b** and **2c**, **4c** was assigned on the basis of NMR. data, cited in Table 2.

Table 2. *Characteristic NMR. Data of the Reaction Products* **2** *and* **4**

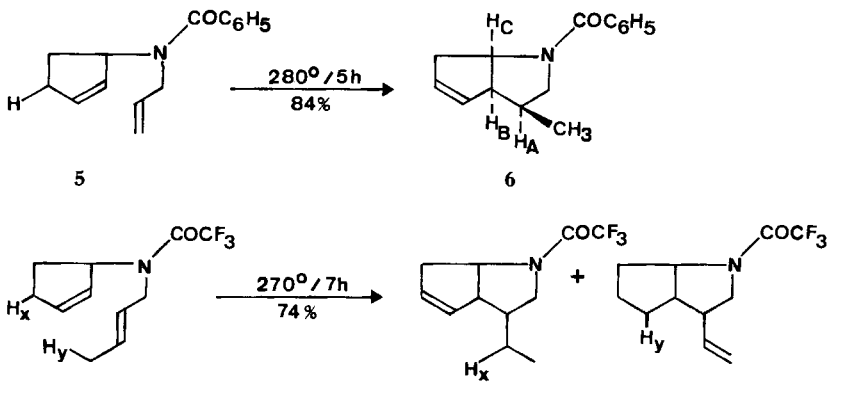
Product	R^1	R^2	R^3	Solvent, Temp.	δ ppm
2a	CH_3	H	H	$(CD_3)_2SO$/120°	0.95 (*d*, $J \sim 7$ Hz, 3H): sec. CH_3
4a	CH_3	H	H	$(CD_3)_2SO$/120°	1.05 (*d*, $J \sim 7$Hz, 3H): sec. CH_3
2b	CH_3	H	C_6H_5	$CDCl_3$/30°	5.8 (*m*, 1H): H_A
4b	CH_3	H	C_6H_5	$CDCl_3$/30°	5.1 (*m*, 1H): H_A
2c	OCH_3	CH_3	H	$CDCl_3$/30°	1.32 (*s*, 3H), 1.38 (*s*, 3H): $C(CH_3)_2$
4c	OCH_3	CH_3	H	$CDCl_3$/30°	1.17 (*s*, 3H), 1.47 (*s*, 3H): $C(CH_3)_2$

Neither an initial *cis-trans*-isomerization **1c** ⇄ **3c**[13]), nor interconversion of the diastereoisomeric products **2c** and **4c** could be established under cyclization conditions[14]). Hence it appears that the stereochemistry of the reaction is kinetically controlled.

Inspection of appropriate models show that the observed stereochemical relationships are consistent with a supra-supra-facial process [9].



The product ratios given in Table 1 indicate that for cyclization of the *cis*-crotylamides **1** the *endo*-transition state **B** is highly strained, and that the unstrained *exo*-transition state **A** leads to the observed *cis*-substituted pyrrolidines **2**. For cyclization of the *trans*-crotylamides **3**, both *endo*- and *exo*-transition states **C** and



5 6 7 8 9

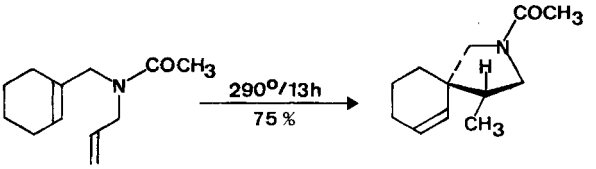
[13]) The thermolysis of the *cis*-crotylamide **1c** was discontinued after 50% conversion. In the regenerated diene no *trans*-crotylamide **3c** could be detected by IR. spectroscopy.

[14]) The separated isomers **2c** and **4c** were kept at 235° for 70 h. No trace of conversion to the isomer was visible on GC.-analysis in either case.

D come into consideration. The observed preference for the *endo* state **C** does not seem to be influenced strongly by the presence of the substituents R^2 and R^3[15]).

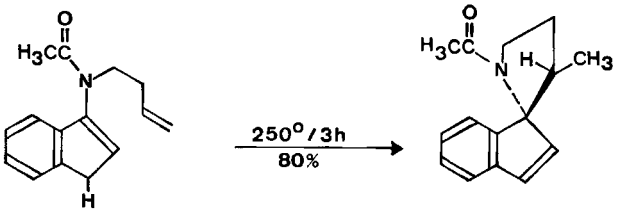
On heating appropriate dienes that contain the ene-component as part of a ring, bicyclic systems may be obtained stereo-specifically in high yields[16]). Thus, the thermal transformation of the diene **5**[17]) to the cyclopenta [b] pyrrole **6** (m.p. 43–45°) represents the stereo-controlled formation of three centers of chirality in a single reaction step. The *cis*-relation of H_A, H_B and H_C, as shown in formula **6**, follows from the NMR. coupling constants $J_{AB} \sim J_{BC} \sim 8$ Hz, observed for the corresponding N-toluenesulfonyl derivative.

Under similar conditions the diene **7**, which contains a *cis*- as well as a *trans*-olefin with allylic hydrogen, cyclized to a 1:1 mixture of the structural isomers **8** and **9**. Consequently H_x must have been transferred as fast as H_y, thus supporting the generalization, that the rate of intramolecular ene-reactions is largely independent of the geometry of the ene-component.



10 **11**

The efficient cyclization of the neat diene **10**[18]) to the pyrrolidine **11** (b.p. 126–129° /0.1 Torr) illustrates a stereospecific approach to spiro-systems. The stereochemical purity of the product **11** was checked by GC. and its configuration was established through X-ray analysis (by *H.-P. Weber*) of the corresponding N,N-dimethyl bromide [13].



12 **13**

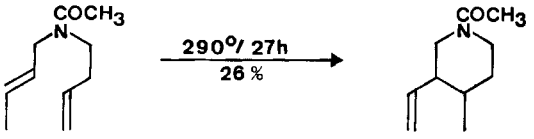
[15]) On thermolysis linalool cyclized preferably to plinols with adjacent methyl and isopropenyl groups in *cis*-position [10].

[16]) Monocyclic 1.6- and 1.7-dienes were reported by *Huntsman et al.* [11] not to cyclize at temperatures up to 500°.

[17]) The neat diene **5** (b.p. 123–126°/0.06 Torr), prepared from N-(cyclopent-2-enyl)-benzamide [12] by subsequent reaction with sodium hydride and allyl bromide, was heated under nitrogen.

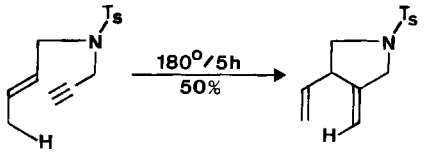
[18]) The diene **10** (b.p. 106°/0.15 Torr) was obtained by refluxing 1-oxaspiro[2,5]octane with 2.5 equiv. of allylamine in water for 22 h, N-acylation of the resulting amino-alcohol with acetic anhydride in dichloromethane/pyridine and dehydration of the acetamide with *p*-toluenesulfonic acid in refluxing toluene for 11 h.

At lower temperatures the neat enamide **12**[19]) rearranged stereospecifically to the spiro-compound **13** (m.p. 117.5–119°). In the NMR. spectrum ($(CD_3)_2SO$/120°) of **13** the CH_3-doublet appears at $\delta = 0{,}56$ ppm and is shifted downfield to $\delta = 0{,}73$ ppm on hydrogenation of the olefinic double bond, thus indicating the *cis*-relationship of the sec. methyl group and the olefinic bond.

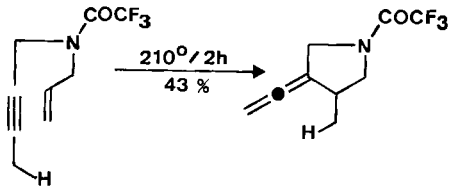


14 **15**

As expected[20]), the cyclization of the butenylamide **14** required higher temperatures to give the piperidine **15**[21]) in low yield.



16 **17**



18 **19**

By contrast, the reactions **16**[22]) → **17** (m.p. 50–53°) and **18**[23]) → **19** proceeded readily under significantly milder conditions. These experiments indicate that acetylenic enophiles[24]) as well as acetylenic "enes" can participate in intramolecular ene-reactions. To summarize, the method described seems to provide an efficient route to various substituted and polycyclic pyrrolidines[25]). Its stereospecificity may

[19]) The enamide **12** was prepared in 40% yield by condensation [14] of indanone with 1-amino-but-3-ene [15], followed by addition of the resulting azomethine to a mixture of 5 equiv. acetic anhydride + 5 equiv. sodium acetate at 0°.

[20]) It has been observed that 1.6-dienes cyclize at lower temperatures than 1.7-dienes [11].

[21]) The reaction gave preferably one stereoisomer, the configuration of which has not yet been established.

[22]) The enyne **16** (m.p. 62–64°) was prepared by alkylation of the sodium salt of *trans*-N-toluene-sulfonylcrotylamide with propargyl bromide.

[23]) Prepared by alkylation of the sodium salt of N-allyl-trifluoroacetamide with 1-chloro-2-butyne.

[24]) The thermal cyclization of 6-octen-1-yne has been described by *Huntsman et al.* [16].

[25]) The new compounds, described in this communication, were characterized by IR. and NMR. spectra, as well as by elemental analyses and/or mass spectra.

be of importance for the synthesis of certain natural products, as exemplified by the following communication [17].

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184. The Total Synthesis of (±) β-Acorenol[1]

Preliminary Communication[2]

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(4. VI. 73)

Zusammenfassung. Die erste Totalsynthese des Spiro-sesquiterpenes β-Acorenol, ausgehend vom bekannten Cyclohex-1-enylessigsäureäthylester, wird beschrieben. Die Schlüsselstufe **2** → **3** + **4** verläuft über eine thermische intramolekulare En-Reaktion.

β-Acorenol, a spirocyclic sesquiterpene, isolated from the wood of *Juniperus rigida* has been shown by chemical and spectroscopic evidence [1] to have structure **8**[3]. This communication describes the first total synthesis of racemic β-acorenol **8** and β-acoradiene **9** [1], the key step of which utilizes recent observations on the stereocontrolled synthesis of five-membered ring systems [4][4].

The known ethyl cyclohex-1-ene-1-acetate **1** [5] was alkylated [6] with 1-bromo-3-butene to give the oily diene **2**[5][6] (b.p. 91–92°/0.3 Torr; IR.: 1730 cm^{-1}). The latter cyclized in toluene (19% solution in a sealed ampoule) at 280° with 3 days[7] to a 1:1 mixture (65% yield) of the esters **3**[5][6] and **4**[5][6], which were separated by

[1] Presented in part at the International Symposium: «Neue Methoden der Organischen Synthese», Basle, Switzerland, May 11, 1973.
[2] The content of this communication will appear as part of a full paper in this journal.
[3] For isolation and structure of the closely related alaskenes see [2].
[4] For previous approaches to acorane-type compounds see [3] [8].
[5] The IR.- and NMR.-spectra were in agreement with the assigned structure.
[6] Satisfactory elemental analytical data were obtained for this substance.
[7] 1-(5-methyl-4-hexenyl)-cyclohexene is reported not to cyclize at temperatures up to 500° [7].