Tetrahedron Letters,Vol.27,No.16,pp 1767-1770,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

ASYMMETRIC INDUCTION IN INTRAMOLECULAR ENE REACTIONS OF 1,7-DIENES

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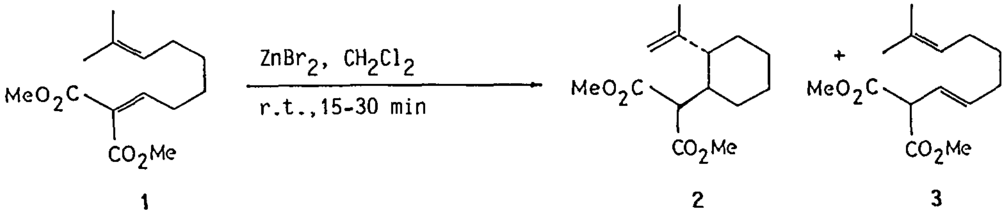
Abstract. Chiral, double-activated enophiles in 1,7-dienes **6a** - **d** undergo thermal and Lewis-acid catalyzed intramolecular ene reactions yielding trans-cyclohexanes **7a-d** and **8a-d**. The extent of diastereoselectivity depends on the reaction temperature. The 1,7-dienes **6** are obtained via Knoevenagel condensation of citronellal **5** with acyclic 1,3-dicarbonyls and analogous compounds **4**. Starting with the diene **6e**, however, an intramolecular hetero-Diels-Alder reaction takes place.

The ene reaction offers a valuable method for carbon-carbon bond formation, though its synthetic power is often severely hindered by modest yields and low selectivity. A detailed study of its intramolecular mode is still wanting. However, there are reasonable results in the case of 1,6-dienes, whereas so far reactions of 1,7-dienes have not been feasible [1]. We have been able to show recently that alkylidene-1,3-dicarbonyls may serve as highly reactive enophiles in a non-induced [2] intramolecular ene reaction of 1,7-dienes yielding trans-substituted cyclohexanes with de >98% [3,4]. Thus, the zinc bromide catalyzed reaction of the double-activated 1,7-dienes **1**, e.g., in a non-induced mode exclusively gives the trans-substituted cyclohexane derivative **rac-2** in 88% yield at room temperature within 15-30 min. There was no trace of the cis-substituted product. In addition, 4% of the isomerized Knoevenagel compound **3** could be isolated.



Apart from these mild reaction conditions, it is of particular value with this and related reactions that the starting materials are easily accessible by simple Knoevenagel condensation of unsaturated aldehydes and 1,3-dicarbonyl compounds. This is why the newly developed ene reaction is a valuable complement to the well-established intramolecular hetero-Diels-Alder cycloaddition of alkylidene- and arylidene 1,3-dicarbonyls [5].

In this paper we describe the asymmetric induction in intramolecular ene reactions of 1,7-dienes. Citronellal **5** served as a starting aldehyde, which has one chiral center and can be obtained in both enantiomeric forms with high enantiomeric purity [6]. Condensation of citronellal **5** [7] with the 1,3-dicarbonyl and analogous compounds **4** in the presence of piperidinium acetate (0.1 eq., r.t., 1h) gives the sensitive alkylidene 1,3-dicarbonyl compounds **6** in nearly quantitative yields (Table 1).

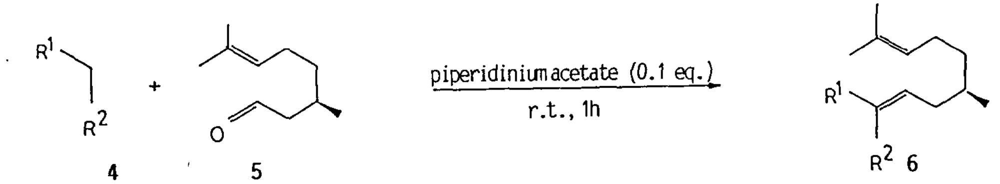
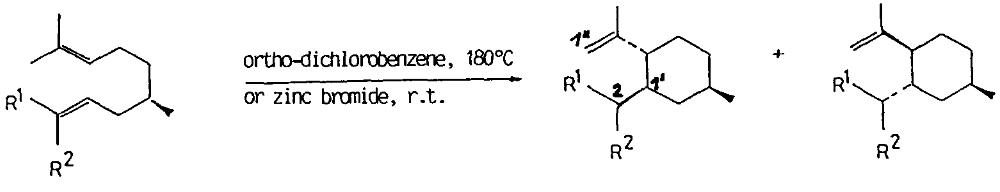


Table. 1. Knoevenagel condensation of citronellal **5** with 1,3-dicarbonyls and analogous compounds

educts	R^1	R^2	products	yield (p.a.-6) %
4a	CO_2Me	CO_2Me	**6a**	82
4b	CO_2Et	CO_2Et	**6b**	84
4c	CN	CN	**6c**	84
4d	CO_2Me	CN	**6d**	90
4e	COMe	COMe	**6e**	87

It is a special advantage of these reactions that the 1,7-dienes obtained can be used in the subsequent ene reactions without further chromatographic purification. The configuration of the newly established double bond in **6** was determined by means of ^{13}C, ^1H-coupling constants [8].

Refluxing of **6a** in ortho-dichlorobenzene yields 75% of the two diastereomeric trans-substituted cyclohexane derivatives **7a** and **8a** [9] in a 86:14 ratio. In this reaction the non-induced diastereoselectivity amounts to 98% (ni-de 98%), since cis-substituted cyclohexanes could not be detected; whereas the induced diastereoselectivity is 72% (i-de = 72 %). However, the ene reaction may also be performed at room temperature in dichloromethane or benzene within 15-30 min using 1.1 equivalents zinc bromide as a Lewis acid catalyst. In this case a 96.5:3.5 ratio of **7a** to **8a** [9] is obtained (ni-de 98%; i-de = 93%) (Table 2). The induced diastereoselectivity of this reaction increases to 96 % when diethylaluminium chloride is applied at -45°C instead; due to the formation of by-products the chemical yields are lower, though.



6 7 8

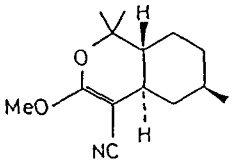
Table 2. Thermal and Lewis acid catalyzed reactions of **6a** - **6e**

	products (isolated yields %)			
		ratio		ratio
educts	180°C (o-DCB)	7 : 8	$ZnBr_2$, r.t.	7 : 8
6a	**7a**[a], **8a**[a] (75)	86 : 14	**7a**[a], **8a**[a] (86)	96.5 : 3.5
6b	-	-	**7b**, **8b** (83)	96.5 : 3.5
6c	**7c**, **8c** (90)	87 : 13	**7c**, **8c** (88)	95.0 : 5.0
6d	**7d**[b], **8d** (89)	88 : 12	**7d**[b], **8d** (19); **9d**, **10d** (68)	96.5 : 3.5
6e	**11e**, **12e** (81)	-	**11e**, **12e** (88)	-

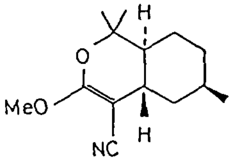
[a] ^{13}C NMR ($CDCl_3$, 50.3 MHz) of **7a/8a**: δ = 18.96/19.36 (C-3"), 22.54/17.89 (5'C-Me), 32.35/26.27 (C-3'), 32.73/27.32 (C-5'), 34.68/31.09 (C-4'), 36.59/33.47 (C-6'), 39.88/34.33 (C-1'), 48.68 (C-2'), 51.80 and 52.22 (O-Me), 53.22/53.44 (C-2), 112.43/112.22 (C-1"), 147.52 (C-2"), 169.03 and 170.11/169.95 (C-1 and C-3).

[b] **7d** was obtained as a 1:8 mixture of stereoisomeres relative to C-2.

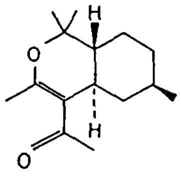
Similar results were obtained with **6b** and **6c** [10]. **6d** yields the cyclohexanes only in the case of the thermal cyclization. The Lewis acid catalyzed reaction leads to the formation of the benzopyran derivates **9d** and **10d** as main products via an intramolecular hetero-Diels-Alder reaction, while the ene-products **7d** and **8d** are obtained in low yields only. **6e** behaves differently in that we find the Diels-Alder products **11e** and **12e** but not those of the ene reaction in the thermal as well as in the Lewis acid catalyzed reaction [11].



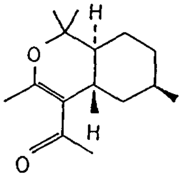
9d



10d



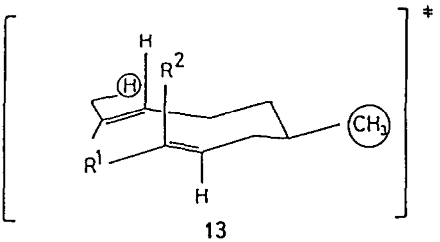
11e



12e

Evidence for the trans-orientation of the substitutents in the ene-products **7** and **8** is provided by the ^1H- and ^{13}C NMR spectra. Thus, we find a coupling constant of J = 11.5 Hz for the 1'H-2'H-coupling as it is to be expected for trans-diequatorially substituted cyclohexanes.

The high selectivity of these ene reactions can be explained by assuming a cyclohexane-like transition state with a chair-arrangement of the chain, where the 1,7-diene is in an exo-E-anti-conformation with either pseudoequatorial **13** or pseudoaxial **14** orientation of the methyl group. The dependence of the ratio of diastereoisomeres on the reaction temperature is in accordance with a $\Delta\Delta G^{\ddagger}$-value of 1.7 kcal/mol at 20°C which in turn corresponds to the difference of the conformational free energies of the methyl group in methylcyclohexane [12]



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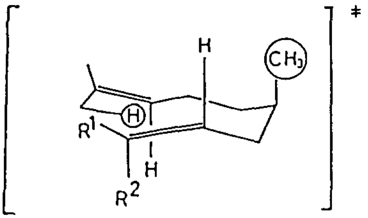

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Acknowledgement. Financial support was granted by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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2 Reactions that preferably form one of several possible chiral diastereomeric (racemic) products out of achiral educts in an achiral environment will henceforth be called "non-induced diastereoselective" and, for reactions under the influence of one or more chiral elements the term "induced diastereoselective" will be used. See ref. 3.

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6 a) For (R)-(+)-citronellal see J. Plessek, Collect.Czech.Chem.Commun. **22** (1957), 644 and J. Fujiwara, Y. Fukutani, M. Hasegawa, K. Maruoka, H. Yamamoto, J.Am.Chem.Soc. **106** (1984), 5004. b) For (S)-(-)-citronellal see M. Hirama, T. Noda, S. Ito, J.Org.Chem. **50** (1985), 127.

7 Here, the configuration relating to (R)-(+)-citronellal is given.

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9 Selectivity of the reactions was determined by means of GLC-MS-coupling and ^{13}C-NMR spectroscopy of the crude products.

10 Apart from **7c** and **8c** small amounts of by-products of unknown structure have been detected.

11 In addition, a decaline derivate could be detected in small amounts which may possibly be formed via a tandem-ene reaction.

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(Received in Germany 16 January 1986)