for their generous support of our program.

Registry No. **1a**, 120741-70-0; **1b**, 120741-71-1; **1c**, 120741-72-2; **1d**, 120741-73-3; **1e**, 120741-86-8; **1f**, 120741-86-8; **1j**, 120741-75-5; **1k**, 120741-76-6; **2a**, 120741-77-7; **2b**, 120741-78-8; **2c**, 120741-79-9; **2d**, 120741-80-2; **2e**, 120741-81-3; **2f**, 120741-82-4; **2g**, 120741-83-5; **2h**, 120741-84-6; **2i**, 120741-85-7; **3a**, 120741-88-0; **3b**, 120741-90-4; **3c**, 120741-92-6; **3d**, 120741-94-8; **3e**, 120741-95-9; **3j**, 120741-97-1; **3k**, 120741-99-3; **4a**, 120741-89-1; **4b**, 120741-91-5; **4c**, 120741-93-7; **4d**, 120771-34-8; **4e**, 120741-96-0; **4f**, 120741-87-9; **4g**, 120742-02-1; **4h**, 120742-03-2; **4i**, 120742-04-3; **4j**, 120741-98-2; **4k**, 120771-24-6; **17**, 120742-05-4; **19**, 120742-01-0; (2*R**,3*S**)-2,3-epoxyhexanol, 90528-63-5; methyl 2-[(tributylstannyl)methyl]-2-propenesulfonate, 120742-00-9.

Asymmetric Induction in Intramolecular Ene Reactions of Chiral 1,7-Dienes: A Diastereo- and Enantioselective Synthesis of Substituted Cyclohexanes[1]

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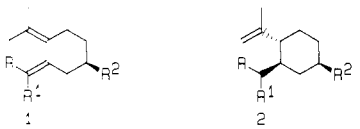
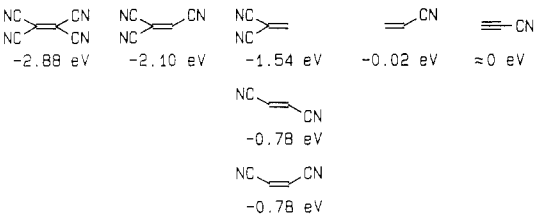
The asymmetric induction in intramolecular thermal and Lewis acid catalyzed ene reactions of chiral 1,7-dienes **9** activated by two electron-withdrawing groups on the enophile is studied. The cycloadducts resulting from intramolecular ene, sequential ene, and hetero-Diels–Alder reactions are characterized and the ratio of the diastereomers obtained is determined. Knoevenagel condensation of citronellal (**8**) with acyclic 1,3-dicarbonyl and analogous compounds **7** gave the corresponding 1,7-dienes **9**, which cyclized under thermal conditions and with $ZnBr_2$ to the trans-substituted ene products **15** and **16**, the hetero-Diels–Alder products **17** and **18**, and the sequential ene products **19** and **20**, depending on the electron-withdrawing groups at the terminus. Derivatives of malonate **9a–c** led exclusively to **15** and **16**, whereas those of acetylacetone **9f** gave **17b** and **18b**. Lewis acid catalyzed reaction of **9g/9h** afforded mainly **19b**. The ratio of the diastereomeric pairs **15/16**, **17/18**, and **19/20** with de values = 74.0–84.0% at 180 °C and 82.0–95.0% at 25 °C is governed by the preference of an equatorial orientation of the methyl group at C-5 in the proposed chairlike transition state and the steric demand of the electron-withdrawing groups in the enophile. The ene adducts are of value as decalin precursors in the synthesis of natural products.

The development of regio- and stereoselective C–C bond-forming reactions is a key objective in organic synthesis. The intramolecular ene reaction has recently received considerable attention[2] and offers a valuable method for the formation of carbo- and heterocyclic cyclopentanes.[2,3] However, with unreactive enes and enophiles, the ene reaction is unsatisfactory, since harsh reaction conditions are required and yields and selectivities are generally low. Structurally modified enes[4] and enophiles as well as the elegant activation of the enophile by means of Lewis acids[5] can be useful to increase the reactivity in ene reactions. Applications of these concepts have been proven particularly successful in the diastereoselective formation of cyclopentanes.[2,3]

In the course of an investigation toward the synthesis of enantiomerically pure sesquiterpenoid natural products, we became interested in the diastereoselective formation of trans-substituted cyclohexanes of type **2**. Retrosynthetic analysis shows that it should be possible to synthesize cyclohexanes **2** by intramolecular ene reactions of 1,7-dienes **1**. In contrast to the intramolecular ene reaction of 1,6-dienes, little is known about this type of ene reaction. To our knowledge, the first example of an intramolecular ene reaction of a 1,7-diene was reported by Huntsman et al.[6] Reaction of **3** at 490 °C yielded disubstituted cyclohexane **4** in 25% yield probably as a mixture of diastereomers. From this and other studies[2,6] on the intramolecular ene cyclization of 1,7-dienes, it is clear that thermal ene reactions of nonactivated 1,7-dienes proceed non-



Scheme I. LUMO Energies of Selected Alkenes and Alkynes[8] (1 eV = 96.5 kJ = 23 kcal)



† Beifuss, U. Thesis, Göttingen, 1987.

(1) Intramolecular Ene Reactions. 7. For part 6, see ref 23.

(2) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (c) Taber, D. F. *Intramolecular Diels–Alder and Alder Ene Reactions*; Springer Verlag: Berlin, 1984; p 61.

(3) (a) Oppolzer, W.; Robbiani, C.; Bättig, K. *Tetrahedron* **1984**, *40*, 1391. (b) Oppolzer, W.; Cunningham, A. F. *Tetrahedron Lett.* **1986**, *27*, 5467. (c) Oppolzer, W.; Nakao, A. *Tetrahedron Lett.* **1986**, *27*, 5471.

(4) (a) Edwards, J. H.; McQuillin, F. J. *J. Chem. Soc., Chem. Commun.* **1977**, 838. (b) Lehmkuhl, H.; Reinehr, D. *J. Organomet. Chem.* **1970**, *25*, C-47. (c) Felkin, H.; Umpleby, J. D.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.* **1972**, 2285. (d) Oppolzer W.; Gaudin, J. M. *Helv. Chim. Acta* **1987**, *70*, 1477.

(5) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426 and references cited therein.

(6) Huntsman, W. D.; Lang, P. C.; Madison, N. L.; Uhrick, D. A. *J. Org. Chem.* **1962**, *27*, 1983.

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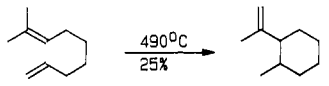
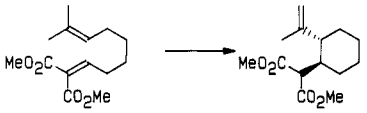


3 4

diastereoselectively and only at high temperatures.

However, frontier orbital analysis indicates that the rate of the ene reaction should be dramatically increased by introducing electron-withdrawing groups at the enophile because of lowering of the LUMO energy[7] (see Scheme I). We have found that two electron-withdrawing groups at the enophile are most effective if they are situated at the terminal carbon.

Another advantage of this type of enophile is also its easy accessibility by Knoevenagel condensation of a 1,3-dicarbonyl and an aldehyde. With this enophile the reaction temperature can be lowered even more by performing the reaction in the presence of Lewis acids. Using this concept we have recently shown that alkylidene 1,3-dicarbonyls may be employed as highly reactive enophiles in both thermal and Lewis acid catalyzed ene reactions. Thus the thermal as well as the zinc bromide catalyzed cyclization of the alkylidenemalonate **5**, for example, produced the trans-substituted cyclohexane **6** in good yield and with excellent noninduced diastereoselectivity.[9]



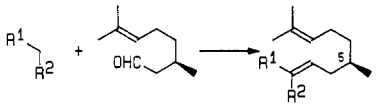
5 6

As far as we know only few stereochemical studies on the intramolecular type I ene reaction of 1,7-dienes[9] and no studies on the asymmetric induction in this type of reaction have been published so far.[10]

Asymmetric induction in intramolecular ene reactions can be brought about by a stereogenic center on the ene, the chain, or the enophile. The use of chiral catalysts[11] and chiral solvents offers another possibility. Here we present our results on the thermal and Lewis acid catalyzed ene reaction of double-activated 1,7-dienes carrying a stereogenic center at C-5.

Results

Preparation of the Chiral 1,7-Dienes. The required chiral alkylidene-1,3-dicarbonyl compounds **9** were obtained by condensation of (*R*)-citronellal (**8**)[12] with acyclic 1,3-dicarbonyls and their analogues **7** with piperidinium acetate as a catalyst and methylene chloride or acetic acid as solvent; the reaction of **7a–g** with (*R*)-citronellal (**8**)

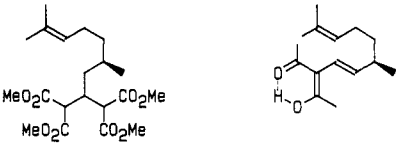


7 8 9

7, 9	a	b	c	d	e
R^1	CO_2Me	CO_2Et	CO_2Bzl	CN	CO_2Me
R^2	CO_2Me	CO_2Et	CO_2Bzl	CN	CN

7, 9	f	g	h	i
R^1	$COCH_3$	CO_2Me	$COCH_3$	CO_2H
R^2	$COCH_3$	$COCH_3$	CO_2Me	CN

yielded the sensitive alkylidene compounds **9** under mild conditions and in high yield. The alkylidenes could be employed without further purification for the cyclization experiments. Prolonged reaction time and/or a large excess of the 1,3-dicarbonyl compounds favored the formation of Michael adducts. Thus, we were able to isolate **10**



10 11

in 95% yield by using a 10-fold excess of **7a**. Unlike alkylidene compounds of cyclic 1,3-dicarbonyls[13] the alkylidene derivatives of acyclic 1,3-dicarbonyls proved to be remarkably stable. This allowed the investigation of their physical and chemical properties. Although the compounds could be isolated and purified chromatographically, distillation was not possible since cyclization took place to some extent. Dienes **9e**, **9f**, **9g**, **9h**, and **9i** underwent ene and/or hetero-Diels–Alder reactions at

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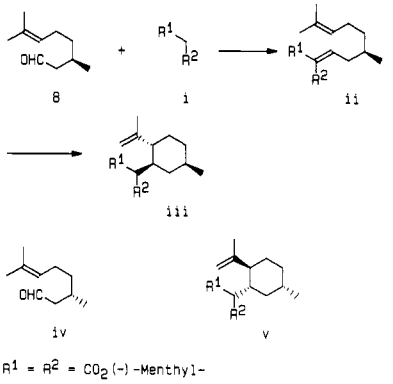
(8) (a) Houk, K. N.; Munchausen, L. L. *J. Am. Chem. Soc.* **1976**, *98*, 937. (b) Bock, H.; Stafast, H. *Chem. Ber.* **1972**, *105*, 1158. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(9) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1042. (b) Tietze, L. F.; Beifuss, U. *Liebigs Ann. Chem.* **1988**, 321.

(10) A communication of parts of this study has already been published, see: Tietze, L. F.; Beifuss, U. *Tetrahedron Lett.* **1986**, *27*, 1767. After the completion and preliminary communication of the present study, Prof. B. B. Snider kindly informed us that similar thermal cyclizations have been investigated by D. A. Uhrick (Uhrick, D. A. Dissertation, Ohio State University, 1972). For a study of the Lewis acid catalyzed hetero ene reaction of 1,7-enal (*R*)-citronellal (**8**), see: Nakatani, Y.; Kawashima, K. *Synthesis* **1978**, 147.

(11) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2203.

(12) (*R*)-Citronellal (**8**) was obtained from Dragoco, Holzminden (FRG). The enantiomerical purity of **8** was checked by ^1H NMR analysis of the diastereochemical purity of the ene product iii, which was obtained by the sequence shown (**8** + i → ii → iii). Control experiments have been



8 i ii iii iv v

$R^1 = R^2 = CO_2(-)$-Menthyl-

performed using (*S*)-citronellal (iv) and racemic (*R,S*)-citronellal. The experiment with (*R*)-citronellal (**8**) afforded a 95:5 ratio of the diastereomeric ene products iii and v. In the control experiment with (*R,S*)-citronellal we found iii and v in a 49:51 ratio and in the experiment with (*S*)-citronellal iv only v was obtained. The diastereomeric ratio of the chromatographically separable iii and v was determined by integration of the signal for H-2 at $\delta = 3.40$ and $\delta = 3.48$, respectively.

(13) Tietze, L. F. In *Selectivity-a Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Weinheim, 1984; p 299.

Table I. Thermal Cyclization of 9 at 180 °C

educts	R^1	R^2	reactn time, h	ene products	yield, %	ratio 15/16	i-de,[a] %	hetero-Diels–Alder adducts	R^1	R^2	yield, %	ratio 17/18[d]	i-de,[a] %
9a	CO_2Me	CO_2Me	7	**15a/16a**	75	89.7:10.3 (±0.1)[b]	79.4	–					
9c	CO_2Bzl	CO_2Bzl	8	**15c/16c**	66	91.5:8.5 (±0.2)[b]	83.0	–					
9d	CN	CN	1	**15d/16d**	90[c]	87:13[d]	74.0	–					
9e	CO_2Me	CN	2.5	**15e/16e**	89[e]	88.3:11.7, (±0.1)[b,f]	76.6	–					
9f	$COCH_3$	$COCH_3$	1	*g*				**17b/18b**	CH_3	$COCH_3$	81[g]	89:11	78.0
9g/9h	CO_2Me	$COCH_3$	2	**15g/16g**	7	–		**17c/18c**	CH_3	CO_2Me	72	91:9	82.0
9g	CO_2Me	$COCH_3$	1.5	**15g/16g**	32	–		**17c/18c**	CH_3	CO_2Me	45	92:8	84.0
9h	$COCH_3$	CO_2Me	0.75	**15g/16g**	8	–		**17c/18c**	CH_3	CO_2Me	71	90:10	80.0

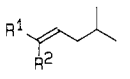
[a] Induced diastereoselectivity (i-de) is calculated to one decimal place. [b] Calculated from GLC data, standard deviation in parentheses. [c] In addition, 8% of **24** was detected (GLC). [d] Calculated from ^{13}C NMR data. [e] **15e** was obtained as a 88:12 mixture of stereoisomers relative to C-2. [f] Ratio was determined by GLC after conversion into **27/28**. [g] 9% of a mixture of **19a** and **20a** was isolated, and in addition, 5% of **15f** was detected (^{13}C NMR).

Table II. Zinc Bromide Catalyzed Cyclizations of 9 at 25 °C

educts	R^1	R^2	ractn time, min	ene products	yield, %	ratio 15/16	i-de,[a] %	hetero-Diels–Alder adducts	R^1	R^2	yield, %	ratio 17/18	i-de[a], %
9a	CO_2Me	CO_2Me	15–30	**15a/16a**	86	96.6:3.4 (±0.2)[b]	93.2	–					
9b	CO_2Et	CO_2Et	15–30	**15b/16b**	83	96.9:3.1 (±0.1)[b]	93.8	–					
9c	CO_2Bzl	CO_2Bzl	45–60	**15c/16c**	79	97.5:2.5 (±0.1)[b]	95.0	–					
9d	CN	CN	90–105	**15d/16d**	88	94.2:5.8 (±0.1)[b]	88.4	–					
9e	CO_2Me	CN	60	**15e/16e**[c,d]	19	96.3:3.7 (±0.2)[b,e]	92.6	**17a/18a**	OMe	CN	68[d]	91:9[f]	82.0
9f	$COCH_3$	$COCH_3$	30	–				**17b/18b**	CH_3	$COCH_3$	86[g]	94.6:5.4 ±(0.2)[h]	89.2
9g/9h	CO_2Me	$COCH_3$	30	**15g/16g**	9[i]	–		**17c/18c**	CH_3	CO_2Me	18[i]	96:4[f]	92.0

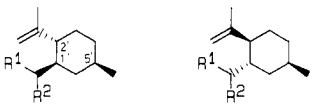
[a] Induced diastereoselectivity (i-de) is calculated to one decimal place. [b] Calculated from GLC data, standard deviation in parentheses. [c] **15e** was obtained as a 87:13 mixture of stereoisomers relative to C-2. [d] In addition, 3–8% of a mixture of **33/34** was isolated. [e] Ratio was determined by GLC after conversion into **27/28**. [f] Calculated from ^{13}C NMR data. [g] In addition 7% of a mixture of **19a** and **20a** was isolated. [h] Calculated from HPLC data. [i] In addition, 45% of a mixture of **19b/20b** (96:4) and 20% of **32** were isolated.

room temperature (50–75% conversions) when kept for a longer period (2 months). Alkylidenemalonates such as **9a** were the only compounds that did not cyclize under these conditions. All of these alkylidene compounds partially isomerized to the β,γ-unsaturated isomers on storage at room temperature according to NMR spectroscopy. Similar isomerizations have been reported by Verhé[14a] and Yamanaka.[14b] In general, separation of the β,γ-unsaturated isomers from the α,β-unsaturated isomers was impossible due to their similar chromatographical behavior. Only **11**, owing to its chelation properties, could be separated from **9f**. In connection with mechanistic investigations it was of particular importance to determine the configuration of the alkylidene double bond in **9e**, **9g**, and **9h**. This was achieved by analysis of the vicinal ^{13}C, ^1H coupling constants.[15] Reaction of **8** with cyanoacetic ester **7e** yielded only one of two possible double-bond isomers, namely, **9e**, whereas the reaction with **7g** produced isomers **9g** and **9h** in a ratio of 35:65, which could be separated by column chromatography. While the configuration of the alkylidene double bond in **9e** proved stable at room temperature, isomerization of **9g** and **9h** was observed after a few hours at 0 °C. This result was corroborated by isomerization experiments with the model compounds **12**, **13**, and **14**. We found the double bond in **12** to be stable at room temperature as well as at 180 °C, while the double bond in **13** and **14** respectively isomerized at room temperature within 3 days and at 180 °C within 1 h.



	R^1	R^2
12	CO_2Me	CN
13	CO_2Me	$COCH_3$
14	$COCH_3$	CO_2Me

Thermal and Lewis Acid Catalyzed Cyclizations of Chiral 1,7-Dienes 9. The thermal cyclization of the chiral alkylidene-1,3-dicarbonyls **9** was performed in boiling *o*-dichlorobenzene at 180 °C (Table I) and the Lewis acid catalyzed reaction at 25 °C by using zinc bromide in methylene chloride or benzene (Table II). Depending on the nature of the electron-withdrawing groups in the enophile either ene products **15** and **16**, hetero-Diels–Alder adducts **17** and **18**, or sequential ene products **19** and **20** were obtained.



15 16

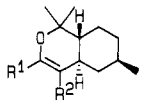
15, 16	a	b	c	d	e
R^1	CO_2Me	CO_2Et	CO_2Bzl	CN	CO_2Me
R^2	CO_2Me	CO_2Et	CO_2Bzl	CN	CN
15, 16	**f**	**g**	**h**	**i**	
R^1	$COCH_3$	CO_2Me	$COCH_3$	CO_2H	
R^2	$COCH_3$	$COCH_3$	CO_2Me	CN	

In a kinetically controlled reaction, both the thermal and zinc bromide catalyzed transformation of **9a–c** exclusively

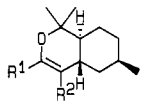
(14) (a) Verhé, R.; DeKimpe, N.; Courtheyn, D.; DeBuyck, L.; Schamp, N. *Tetrahedron* **1982**, *38*, 3649. (b) Yamanaka, H.; Yokoyama, M.; Sakamoto, T.; Shiraishi, T.; Sagi, M.; Mizugaki, M. *Heterocycles* **1983**, *20*, 1541.

(15) Tietze, L. F.; Beifuss, U., to be published. For $^3J_{CH}$ coupling constants, see: (a) Vogeli, U.; Philipsborn, W. v. *Org. Magn. Reson.* **1975**, *7*, 617. (b) Kingsbury, C. A.; Draney, D.; Sopchik, A.; Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 3863.

gave the trans-substituted ene adducts **15a–c** and **16a–c** with yields ranging from 66 to 75% in the thermal reactions and from 79 to 86% in the catalyzed variant with a ni-de value of >98%. In none of the reactions could the cis isomer be detected. The diastereoselectivity induced by the stereogenic center was found to be i-de = 79.4–83.0% (**15**/**16** = 89.7:10.3–91.5:8.5) for the thermal reaction at 180 °C and i-de = 93.2–95.0% (**15**/**16** = 96.6:3.4–97.5:2.5) for the zinc bromide catalyzed reaction at 25 °C. As expected the selectivity strongly depends on the reaction temperature but also on the steric demand of the ester groups in the enophile.

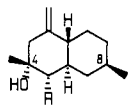


17

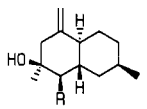


18

17, 18	R^1	R^2
a	OMe	CN
b	CH_3	$COCH_3$
c	CH_3	CO_2Me



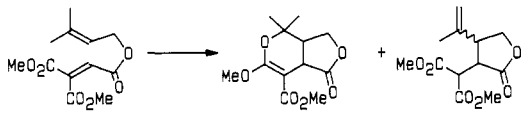
19



20

19, 20	R
a	$COCH_3$
b	CO_2Me

The clean and diastereoselective formation of ene products **15** and **16** from **9** was astounding, since Snider has observed nonstereoselective formation of a 70:30 mixture of hetero-Diels–Alder and ene products **22** and **23**, respectively, at 85 °C and exclusive formation of **23** at 120 °C on heating **21**.[7c] This may be due to the three elec-

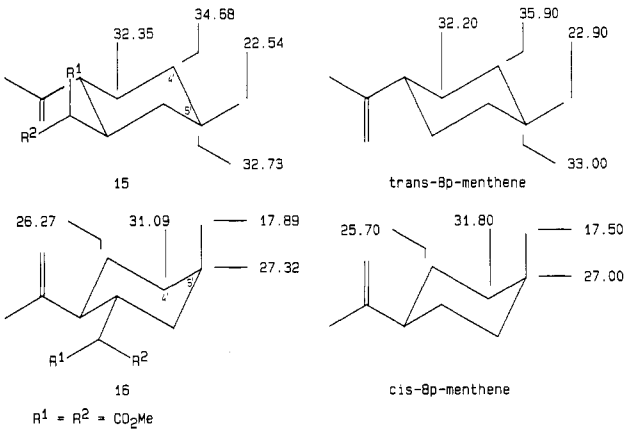


21 22 23

tron-withdrawing groups in **21** compared to the two electron-withdrawing groups at the terminus in our systems.

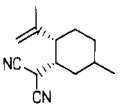
The structure of the ene products was established by ^1H NMR and ^{13}C NMR spectroscopy. For **15a**, with a 1,2-trans-diequatorial arrangement of the substituents, a coupling constant of $J_{1',2'}$ = 11.5 Hz is found. The 1,3-cis-diequatorial arrangement of the methyl group and of the substituent at C-1′ follows from the coupling pattern of 6′-H_{ax}, which shows three couplings of J = 11.5 Hz. The equatorial position of the methyl group follows from its signal at δ = 22.54 in the ^{13}C NMR spectrum. The 1,4-trans-diequatorial arrangement of the methyl and the isopropenyl groups was deduced from a comparison with the ^{13}C NMR spectrum of *trans-p*-menth-8-ene[16] as both compounds exhibit characteristic shifts for C-3′, C-4′, C-5′, and 5′-CH_3 (see Scheme II). For the unseparated **16a** with an axial arrangement of the methyl group at C-5′, an absorption at δ = 17.89 is observed. The 1,4-cis arrangement of the methyl and the isopropenyl group in **16a** can be deduced from a comparison of ^{13}C NMR data with that of *cis-p*-menth-8-ene.[16] Both show significant signals for

Scheme II. Characteristic ^{13}C NMR Shifts in 15a/16a and *trans*- and *cis-p*-Menth-8-ene



C-3′, C-4′, C-5′, and 5′-CH_3 (see Scheme II). A typical feature in the mass spectra of nearly all ene products **15**/**16** is the fragment $C_{10}H_{16}^+$ (m/z 136) formed by a McLafferty rearrangement. The formation of this fragment has been the basis for identification of **15**/**16** via GLC-MS and thus for the determination of the diastereomeric ratio via GLC.

The thermal cyclization of the alkylidenemalonodinitrile **9d** is the only case where we found a small amount of cis-substituted cyclohexane **24** (ni-de = 84.8%, trans/cis = 92.4:7.6) besides the trans-substituted **15d** and **16d** (i-de = 74%). $ZnBr_2$-catalyzed reaction of **9d** for 1.5–1.75 h afforded **15d** and **16d** exclusively (i-de = 88.4%); no cis product could be detected. Stirring **9d** with $ZnBr_2$ for 24 h led to the unexpected formation of the bicyclo[4.2.0]-octanes **25** and **26**. Presumably, the bicyclo[4.2.0]octanes are formed via **15d** and **16d**, since the amount of **25** and **26** increases with the reaction time.



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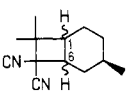


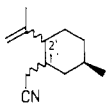
25 : 1R, 6R
26 : 1S, 6S

Thermal cyclization of the alkylidene cyanoacetate **9e** yields solely the trans-substituted ene products **15e**/**16e**, whereas the catalyzed transformation gives mainly the hetero-Diels–Alder products **17a**/**18a** (68%) and only 19% of the ene products **15e**/**16e**. **15e** was obtained as a mixture of C-2 epimers (2*R*:2*S* = 88:12) from which the 2*R* isomer could be separated by crystallization. X-ray analysis enabled us to determine unambiguously the configuration at C-2, which otherwise was not possible. Unfortunately, the stereogenic center C-2 is not stable under the conditions of its formation. Therefore, from the ratio of epimers in **15e** nothing can be concluded about the stereospecificity of the hydrogen transfer in the ene process.

It is important to emphasize that in the Lewis acid catalyzed transformation of **9e** to give **15e**/**16e** and **17a**/**18a**, the ene reaction shows a significantly higher induced diastereoselectivity than the hetero-Diels–Alder reaction (ene:i-de = 92.6%; DA:i-de = 82.0%). At present there is no obvious explanation for this phenomenon. However, this effect will be investigated in some detail in the future. For the determination of the **15e**/**16e** ratio the compounds were transformed to **27** and **28** by demethoxycarbonylation.[17] Trans-substituted hexahydrobenzopyrans

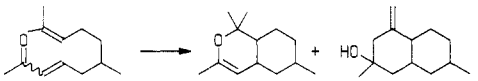
(16) Pekhk, T. I.; Lippmaa, E. T.; Lysenkov, V. I.; Bardyshev, I. I. *Zh. Org. Khim.* **1979**, *15*, 1877.

(17) Krapcho, A. P. *Synthesis* **1982**, 805 and 893.



27 : 1'S, 2'R
28 : 1'R, 2'S

17b/18b were formed nearly exclusively in both the thermal and Lewis acid catalyzed reaction of alkylidene acetylacetonate **9f**. The formation of *cis*-hexahydrobenzopyrans cannot be entirely ruled out; the amount, however, must be below 2%. In addition, a small amount of an interesting decalin derivative **19a/20a** (91:9) was obtained, which is most likely formed by a sequential ene reaction via **15f/16f**. Transformations of a similar single activated compound, citronellideneacetone (**29**), are described in the literature. Naves and Ardizio found that the reaction of **29** with BF_3·OEt_2 gave 63% of hetero-Diels–Alder product **30**[18] without mentioning the diastereoselectivity. On the other hand, Snider reported on



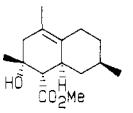
29 30 31

the formation of **30** and **31**[19] from **29**, which showed a strong dependence on the concentration of the catalyst.

The assignment of the relative configuration of the Diels–Alder products **17** and **18** follows from analysis of the chemical shifts and coupling patterns for 4a-H, 5-H_{ax}, and 5-H_{eq}. 5-H_{ax} in **17b** absorbs at δ = 0.68 with three couplings of J = 11.5 Hz; this proves not only the equatorial orientation of the methyl group at C-6 but also the trans-annulation of the rings. 5-H_{eq} shows a typical low-field shift toward δ = 2.14. The methyl group at C-6 absorbs at δ = 0.89, which again shows its equatorial position. The shifts for C-4a (δ = 35.93) and C-8a (δ = 47.87) in the ^{13}C NMR spectrum also prove the trans arrangement of the rings. An X-ray analysis secures the assignment of the relative configuration in **17b**.

Peculiar results were obtained in the transformation of **9g** and **9h** at 180 °C. Reaction of the thermodynamic mixture **9g/9h** as well as pure **9h** afforded ene products **15g,h/16g,h** in 7–8% yield and the hexahydrobenzopyrans **17c/18c** in 71–72% yield. Cyclization of pure **9g** gave four times as much of the ene products. Interestingly, the reaction of **9h** is more than twice as fast as that of **9g** and the mixture **9g/9h**. These results clearly indicate a dependence of the product distribution and the reaction rate upon the configuration of the alkylidene double bond in **9g** and **9h**. Quantitative statements, however, cannot be made for the following reasons: (i) Due to the isomerization experiments with pure **13** and **14**, we have to assume that the configuration at the alkylidene double bond in **9g** and **9h** is not stable under reaction conditions. (ii) The rate of the double-bond isomerization of **9g** and **9h** cannot be measured as they already cyclize under the conditions of isomerization. (iii) Owing to their low stability, the proportion of the ene products cannot be determined with sufficient accuracy. Lewis acid catalyzed reaction of **9g/9h** shows again that the catalyst not only affects the reaction rate but may also change the properties of the enophile. Here the ene (9%) and the Diels–Alder products (18%) are side products and the main products are the trans-annulated decalins **19b/20b** (45%; **19b/20b** = 96:4) and **32**, the latter very likely derived from **19b** by isomerization of the double bond. It is significant that Brønsted acids such as a mixture of acetic and hydrochloric acid effect the stereoselective transformation of **9g/9h** to give hetero-Diels–Alder adducts **17c/18c** in 84% yield (ni-de >98%; i-de = 92%) as the only products.

For the decalins **19/20**, the trans substitution of the rings and the equatorial arrangement of the methoxycarbonyl group can be deduced from the absorption for 7-H_{ax} at δ = 0.80 and its appearance as a quartet with a coupling constant of J = 12.5 Hz as well as from the shift of 5-H_{ax} at δ = 2.29 with a coupling constant of J = 11 Hz. The relative configuration at C-4 was made certain by a W coupling of the hydroxylic proton (δ = 3.24, J = 2 Hz) with 3-H_{ax} (δ = 2.12). The W coupling may only occur if the hydroxy group occupies the axial position at C-4. The assignment has been corroborated by double-resonance experiments and proved by an X-ray analysis of **19b**.



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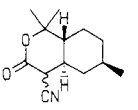
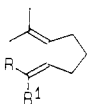


33 : α-CN
34 : β-CN

It is of historical interest that Tiemann already reported the reaction of citronellal (**8**) with cyanoacetic acid (**7i**) in 1899. He obtained a crystalline compound, which he identified as the Knoevenagel adduct **9i**. However, by repeating this reaction we were able to isolate 45% of a crystalline mixture of **33** and **34** (89:11) having a melting point in accordance with that reported by Tiemann.[20]



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Discussion

The ene reaction of 1,6-dienes to give cyclopentane derivatives is a well known and widely used method. In contrast, the formation of cyclohexanes from 1,7-dienes was not feasible so far because of low yields, lack of selectivity, and high reaction temperature.[2,6] However, we found that the use of doubly activated enophiles allows the diastereoselective formation of cyclohexane derivatives in high yields. Another advantage of our procedure is the easy access to the starting material by Knoevenagel condensation of a 1,3-dicarbonyl and an appropriate aldehyde.

In the transformation of the alkylidene-1,3-dicarbonyls **9**, ene, hetero-Diels–Alder, and sequential ene products **15/16**, **17/18**, and **19/20**, respectively, can be obtained. The preferential formation of one of these products clearly depends on the nature of the electron-withdrawing groups in the enophile moiety. With CO_2R and CN groups only ene products are found, whereas with CO groups increased amounts of the hetero-Diels–Alder adduct are obtained.

Alkylidene compounds of type **9** represent, according to Polansky,[21] electrically neutral organic Lewis acids. While the alkylidenemalonic esters **9a–c**, presumably the weakest Lewis acids give ene products exclusively, the alkylideneacetylacetone **9f**, the strongest Lewis acid, undergoes cyclization with almost exclusive formation of hetero-Diels–Alder products. The cyclization of **9d** will have to be viewed as a special case, due to the fact that Diels–Alder products cannot be formed. The cyclizations of **9e**, **9g**, and **9h** clearly show that other still unknown factors play a role

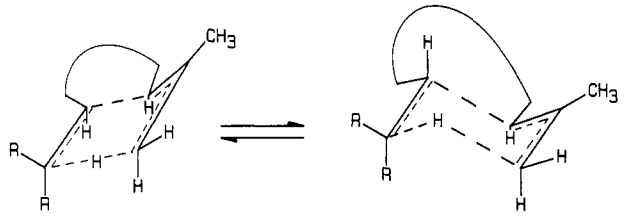
(18) Naves, Y. R.; Ardizio, P. *Bull Soc. Chim. Fr.* **1953**, 494.
(19) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *42*, 4538.
(20) Tiemann, F.; *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 824.
(21) (a) Polansky, O. E. *Mh. Chem.* **1961**, *92*, 820. (b) Polansky, O. E.; Schuster, P. *Mh. Chem.* **1964**, *95*, 281. (c) Kunz, F. J.; Margaretha, P.; Polansky, O. E. *Chimia* **1970**, *24*, 165.

in the competition between ene, hetero-Diels–Alder, and sequential ene reactions.

It should be noted that the formation of the ene and Diels–Alder products is strictly kinetically controlled and a conversion of the ene into the Diels–Alder product or vice versa does not occur under the reaction conditions.

Several suggestions about the probable geometry of the transition state of the ene reaction have been made ranging from the rationals made by Hoffmann[2a] to the STO-3G and 3-21G calculations on the transition structure of the reaction between propene and ethylene recently reported by Houk et al.[22] The latter calculations show that the transition structure can be described as an envelope conformation similar to that of cyclopentane. However, in the intramolecular reaction, the geometry of the connecting chain and the substitution pattern is of great importance.

We believe that the main reason for the highly preferred formation of trans-1,2-disubstitiuted cyclohexanes is a destabilization of the proposed envelope-like transition state with an *endo-E(ene)-syn* arrangement (transition structure A). The destabilization results from a syn-periplanar orientation of the two electron-withdrawing groups and the neighboring substituents. In the case of 1,7-dienes, this would cause a more chairlike transition state of the *exo-E(ene)-anti* type (transition structure B) with a diequatorial arrangement of the connecting four-carbon chain. This proposal is in agreement with the observation that cyclization of the alkylidenemalononitrile **9d** with the two "slim" cyano moieties results in a significantly lower trans selectivity. The great importance of this "sp^2-geminal effect" is corroborated by the ene reaction of 1,6-dienes of type **35** (R = R^1 = CO_2R), which give almost exclusively trans-1,2-disubstituted cyclopentanes.[23] This selectivity contrasts with recent calculations which predict that the parent diene (**35**, R = R^1 = H) will give exclusively cis-1,2-disubstituted cyclopentanes.[22]

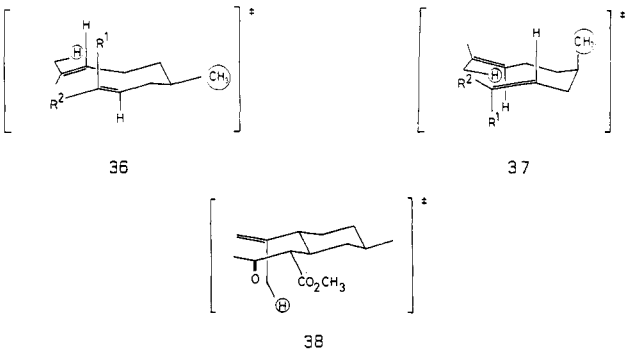


In the preferred *exo-E-(ene)-anti* transition state for the cyclizations of **9**, the methyl group can adopt either the more stable pseudoequatorial orientation **36** to give **15** or the pseudoaxial orientation **37** to give **16**. Similar considerations hold true for the formation of the hetero-Diels–Alder products **17** and **18**. As the ene and hetero-Diels–Alder reactions proceed with kinetic control, the difference of the free activation energies $\Delta\Delta G^{\ddagger}$ of the various reaction paths is responsible for the product distribution. We find that the ratio of diastereomers **15**/**16** in the ene reaction is considerably higher than would be expected from comparison with the conformational free energies of the methyl group in methylcyclohexane (ΔG° = −1.74 kcal/mol).[24] It is also remarkable that the diastereoselectivity induced by the methyl group in the β-position to the enophile moiety is much higher in the ene reaction than it is in the hetero-Diels–Alder reaction. These effects, which cannot be explained at this time, will be further investigated by us.

Table III. $\Delta\Delta G^{\ddagger}$ in Intramolecular Ene Reactions of 1,7-Dienes 9

			$\Delta\Delta G^{\ddagger}$ [kcal/mol][a] at	
educts	R^1	R^2	179.5 °C	25 °C
9a	CO_2Me	CO_2Me	−1.95	−1.98
9c	CO_2Bzl	CO_2Bzl	−2.14	−2.16
9d	CN	CN	−1.71	−1.66
9e	CO_2Me	CN	−1.81	−1.93

[a] Calculated from the ratio of the products **15**/**16**.



It is also of great interest that the ratio of diastereomers improves with the size of the electron-withdrawing groups of the enophile (see Table III), although a direct steric effect cannot be seen by evaluating Dreiding models.

The sequential ene products **19**/**20** are probably formed via **15** and **16**, respectively, by an intramolecular type-2 hetero–ene reaction passing through transition state **38**. This assumption explains the remarkable selectivity resulting in the exclusive formation of the axial hydroxy group. The reaction is one of a few known examples of two successive intramolecular ene reactions.[25] The scope and limitation of this reaction type, which allows the construction of decalin derivatives from easily accessible acyclic precursors, is under active investigation. We assume that this reaction proceeds via a concerted mechanism. In contrast, the Brønsted acid catalyzed cyclization of **9g**/**9h** to the hetero-Diels–Alder products **17c**/**18c** is presumably a cationic cyclization.

Summary

The intramolecular ene reaction of chiral 1,7-dienes activated by two electron-withdrawing groups at the chain terminus has been developed into a method for the synthesis of enantiomerically pure trans-substituted cyclohexane derivatives with high noninduced and induced diastereoselectivity and good to very good yields. This cyclization reaction should prove useful in the synthesis of sesquiterpenoid natural products.

Experimental Section

Instrumentation. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. The following less common NMR abbreviations are used: mc = multiplet centered, br = broad, ax = axial, eq = equatorial. Mass spectra were measured at 70 eV. UV–vis spectra (MeCN, λ_{max}, nm (log ε)) were taken with a Varian Cary 219 spectrometer. Melting points were determined on a Kofler hot stage apparatus and are corrected.

(22) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947.
(23) Tietze, L. F.; Beifuss, U.; Ruther, M.; Rühlmann, A.; Antel, J.; Sheldrick, G. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1186.
(24) Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin Trans. II* **1980**, 255.
(25) For two successive ene reactions, where the first is inter- and the second is intramolecular, see: Snider, B. B.; Goldman, B. E. *Tetrahedron* **1986**, *42*, 2951 and references cited therein.

Analytical GLC was carried out by using the following columns: (1) Chrompack 0.13 μm CpSil 5, 0.32 mm × 25 m fused silica. (2) Macherey, Nagel & Co., 0.25 μm chemical bound SE 30, 0.32 mm × 50 m fused silica. (3) 3% SE 30 on supelcoport (100 – 120 mesh), 2 mm × 2.5 m glass. Analytical HPLC was accomplished with UV detection using the following columns: (1) Knauer Nucleosil 5 CN, 4 mm × 300 mm. (2) Macherey Nagel & Co. Nucleosil CN-10, 4 mm × 300 mm.

Materials. All solvents were distilled prior to use. All reactions were carried out under argon and monitored by TLC (Macherey, Nagel & Co. SIL G/UV_{254}). Products were generally isolated by flash chromatography on SiO_2 (Silica Woelm 32-63 active, Fa. Woelm Pharma, Eschwege).

Knoevenagel Condensation of Aldehyde 8 with 7. General Procedure I. To a stirred solution of aldehydes **8** (10.0 mmol) and **7** (11.0 mmol) in anhydrous methylene chloride (5 mL) were added piperidine (1.00 mmol) and acetic acid (1.00 mmol) at 0 °C. The mixture was stirred at room temperature for 45 min; then again acetic acid (1.00 mmol) and piperidine (1.00 mmol) were added. After being stirred for 15 min, the reaction mixture was evaporated in vacuo, diluted with ether (50 mL), and washed twice with water (2 × 10 mL). The aqueous phases were extracted with ether (3 × 10 mL). The combined etheral phases were successively washed with saturated sodium hydrogen carbonate solution (10 mL), water (10 mL), and brine (10 mL) and dried (Na_2SO_4). After removing the solvent, the crude products were pure enough to be used in further reactions. Analytically pure samples were obtained by column chromatography.

General Procedure II. A stirred solution of aldehydes **8** (10.0 mmol) and 1,3-dicarbonyl compound **7** (11.0 mmol) was treated with acetic acid (25 mL) and piperidine (1.00 mmol) at 0 °C. After 45 min of stirring, a small amount of sodium sulfate or 3-Å molecular sieves was added. Then the reaction mixture was stirred for another 15 min, diluted with ether (25 mL), and washed with water (10 mL) until the aqueous phase was neutral. The collected aqueous phases were extracted with ether (3 × 10 mL). The combined etheral phases were washed with saturated sodium hydrogen carbonate solution (10 mL) and brine (10 mL) and dried (Na_2SO_4). Further workup was as described in general procedure I.

Methyl (5*R*)-2-(Methoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate (9a). Reaction of **7a** with **8** according to general procedure I yielded after chromatography (petroleum ether/acetone, 98:2) 2.20 g (82%) of a sensitive colorless oil: R_f 0.51 (ether/hexane, 1:1); HPLC *t*(**9a**) 3.43 min (column 2; ether/hexane, 1:2; flow 1.5 mL/min); $[\alpha]^{20}_D$ –8.2° (*c* = 1, CH_3CN); IR (film, cm^{-1}) 1730, 1645, 1260, 1225, 1060; UV sh 210 (4.13); ^1H NMR (100 MHz, C_6D_6) δ 0.78 (d, *J* = 6.5 Hz, 3 H, 5-CH_3), 0.94–1.46 (m, 3 H, 5-H, 6-H_2), 1.53 (s br, 3 H, 10-H_3), 1.66 (s br, 3 H, 9-CH_3), 1.91 (q m, *J* = 7 Hz, 2 H, 7-H_2), 2.13 (mc, 2 H, 4-H_2), 3.39 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 5.10 (tm, *J* = 7 Hz, 1 H, 8-H), 7.06 (t, *J* = 8 Hz, 1 H, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ 17.66 (C-10), 19.59 (5-CH_3), 25.81 (9-CH_3), 25.81 (C-7), 32.68 (C-5), 36.99 and 37.03 (C-4 and C-6), 51.69 and 51.81 (OCH_3), 124.89 (C-8), 129.80 (C-2), 131.25 (C-9), 148.48 (C-3), 164.20 (2-CO), 165.76 (C-1); MS *m*/*z* 268 (1, M^+), 237 (2, M – CH_3O), 136 (47, $C_{10}H_{16}$). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.19; H, 9.03.

Methyl (5*R*)-2-(Methoxycarbonyl)-3-(dimethoxymalonyl)-5,9-dimethyldec-8-enoate (10). A solution of **9a** (268 mg, 1.00 mmol) and **7a** (1.32 g, 10.0 mmol) in methylene chloride (1 mL) treated with piperidine (85 mg) was stirred for 1 h at room temperature. The reaction mixture was evaporated in vacuo, diluted with ether (25 mL), washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. Yield after chromatography (ether/hexane, 1:4): 380 mg (95%) of a colorless and viscous oil; R_f 0.33 (ether/hexane, 1:1); $[\alpha]^{20}_D$ –8.6° (*c* = 1, CH_3CN); IR (film, cm^{-1}) 1760, 1740, 1160; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6 Hz, 3 H, 5-CH_3), 0.98–1.80 (m, 5 H, 4-H_2, 5-H, 6-H_2), 1.60 (s br, 3 H, 10-H_3), 1.68 (s br, 3 H, 9-CH_3), 1.96 (mc, 2 H, 7-H_2), 3.02 (mc, 1 H, 3-H), 3.75 (s, 12 H, OCH_3), 3.77 (signal partially masked), 1 H, 2-H or 2′-H), 3.84 (d, *J* = 6 Hz; 1 H, 2H-, or 2′-H), 5.09 (t m, *J* = 7 Hz, 1 H, 8-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.66 (C-10), 19.22 (5-CH_3), 25.37 (C-7), 25.71 (9-CH_3), 30.23 (C-5), 35.75 (C-3), 36.99 and 37.30 (C-4 and C-6), 52.38, 52.48, 52.51, 52.69, 52.77 and 53.21 ($CH(CO_2CH_3)_2$), 124.59 (C-8), 131.30 (C-9), 168.85, 168.89 and 168.98 (CO_2CH_3); MS *m*/*z* 400 (29, M^+), 369 (22, M – CH_3O). Anal. Calcd for $C_{20}H_{32}O_8$: C, 59.99; H, 8.05. Found: C, 60.23; H, 8.04.

Ethyl (5*R*)-2-(Ethoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate (9b). Reaction of **7b** with **8** according to general procedure I yielded after chromatography (petroleum ether/acetone, 98:2) 2.49 g (84%) of a sensitive oil: R_f 0.58 (ether/hexane, 1:1); HPLC *t*(**9b**) 2.45 min (column 2; ether/hexane, 1:1; flow 1.5 mL/min); $[\alpha]^{20}_D$ –8.3° (*c* = 1, CH_3CN); IR (film, cm^{-1}) 1725, 1645, 1260, 1225, 1065; UV sh 210 (4.18); ^1H NMR (100 MHz, C_6D_6) δ 0.52–1.70 (m, 3 H, 5-H, 6-H_2), 0.78 (d, *J* = 6.5 Hz, 3 H, 5-CH_3), 0.92 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 1.02 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 1.52 (s br, 3 H, 10-H_3), 1.64 (s br, 3 H, 9-CH_3), 1.90 (q m, *J* = 7 Hz, 2 H, 7-H_2), 2.17 (mc, 2 H, 4-H_2), 3.99 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 4.12 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 5.07 (t sept, *J* = 7, 1.5 Hz, 1 H, 8-H), 7.08 (t, *J* = 8 Hz, 1 H, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ 14.18 and 14.27 (OCH_2CH_3), 17.63 (C-10), 19.65 (5-CH_3), 25.78 (9-CH_3), 25.83 (C-7), 32.79 (C-5), 36.88 and 37.16 (C-4 and C-6), 60.84 and 60.96 (OCH_2CH_3), 124.89 (C-8), 130.42 (C-2), 131.19 (C-9), 147.39 (C-3), 163.66 (CO), 165.18 (C-1); MS *m*/*z* 296 (6, M^+), 251 (11, M – C_2H_5O). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.99; H, 9.58.

Benzyl (5*R*)-2-(Benzyloxycarbonyl)-5,9-dimethyldeca-2,8-dienoate (9c). Reaction of **7c** with **8** according to general procedure I yielded after chromatography (ether/petroleum ether, 1:9) 2.78 g (66%) of a colorless and viscous oil: R_f 0.24 (ether/hexane, 1:9); HPLC *t*(**9c**) 31.88 min (column 1; flow 0.6 mL/min); $[\alpha]^{20}_D$ –8.3° (*c* = 1, CH_3CN); IR (film, cm^{-1}) 3080, 3060, 3025, 1725, 1640, 1595, 1255, 1210, 1045, 740, 695; UV sh 204 (2.34); ^1H NMR (200 MHz, C_6D_6) δ 0.70 (d, *J* = 6.5 Hz, 3 H, 5-CH_3), 0.92–1.46 (m, 3 H, 5-H, 6-H_2), 1.51 (s br, 3 H, 10-H_3), 1.65 (m, 3 H, 9-CH_3), 1.86 (mc, 2 H, 7-H_2), 2.11 (mc, 2 H, 4-H_2), 5.03 (s, 2 H, benzyl-CH_2), 5.08 (mc, 1 H, 8-H), 5.12 (s, 2 H, benzyl-CH_2), 6.92–7.30 (m, 11 H, 3-H, H-phenyl); ^{13}C NMR (20 MHz, C_6D_6) δ 17.62 (C-10), 19.47 (5-CH_3), 25.66 (C-7), 25.75 (9-CH_3), 32.52 (C-5), 36.84 and 36.90 (C-4 and C-6), 66.70 and 66.81 (OCH_2), 124.78 (C-8), 128.13, 128.26 and 128.59 (CH-arom.), 129.57 (C-2), 131.06 (C-9), 136.07 and 136.16 (C-arom.), 149.18 (C-3), 163.51 (2-CO), 165.86 (C-1); MS *m*/*z* 420 (0.4, M^+), 329 (2, M – C_7H_7). Anal. Calcd for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 77.10; H, 7.73.

(5*R*)-2-Cyano-5,9-dimethyldeca-2,8-dienenitrile (9d). Reaction of **7d** with **8** according to general procedure II yielded after chromatography (petroleum ether/acetone, 98:2) 1.70 g (84%) of a very sensitive colorless oil: R_f 0.54 (ether/hexane, 1:1); GLC *t*(**9d**) 12.4 min (column 1; 50 °C, 5 °C/min); HPLC *t*(**9d**) 3.67 min (column 2; ether/hexane, 1:2; flow 1.5 mL/min); $[\alpha]^{20}_D$ –14.4° (*c* = 1, CH_3CN); IR (film, cm^{-1}) 3040, 2240, 1605; UV 229 (4.13); ^1H NMR (100 MHz, C_6D_6) δ 0.13–2.39 (m, 7 H, 4-H_2, 5-H, 6-H_2, 7-H_2), 0.44 (d, *J* = 6.5 Hz, 3 H, 5-CH_3), 1.55 (s br 3 H, 10-H_3), 1.71 (s br, 3 H, 9-CH_3), 5.01 (mc, 1 H, 8-H), 6.11 (t, *J* = 8 Hz, 1 H, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ 17.67 (C-10), 19.14 (5-CH_3), 25.54 (C-7), 25.79 (9-CH_3), 32.20 (C-5), 36.56 (C-6), 39.68 (C-4), 90.03 (C-2), 111.13 (C-1), 112.59 (2-CN), 124.23 (C-8), 131.68 (C-9), 168.91 (C-3); MS *m*/*z* 202 (8, M^+), 187 (8, M – CH_3). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.03; H, 8.92; N, 13.97.

Methyl (*E*)-(5*R*)-2-Cyano-5,9-dimethyldeca-2,8-dienoate (9e). Reaction of **7e** with **8** according to general procedure II yielded after chromatography (ether/petroleum ether, 1:3) 2.12 g (90%) of a colorless sensitive oil: R_f 0.55 (ether/hexane, 1:1); GLC *t*(**9e**) 16.42 min (column 1; 50 °C, 5 °C/min); HPLC *t*(**9e**) 4.97 min (column 2; ether/hexane, 1:2; flow 1.5 mL/min); $[\alpha]^{20}_D$ –12.1° (*c* = 1, CH_3CN); IR (film, cm^{-1}) 2235, 1735, 1625, 1285, 1265, 1070; UV 225 (3.20); ^1H NMR (60 MHz, C_6D_6) δ 0.53–2.33 (m, 7 H, 4-H_2), 5-H, 6-H_2, 7-H_2), 0.66 (d, *J* = 6 Hz, 3 H, 5-CH_3), 1.52 (s br, 3 H, 10-H_3), 1.66 (s br, 3 H, 9-CH_3), 3.33 (s, 3 H, OCH_3), 5.05 (mc, 1 H, 8-H), 7.38 (t, *J* = 8 Hz, 1 H, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ 17.67 (C-10), 19.45 (5-CH_3), 25.76 (C-7), 25.76 (9-CH_3), 32.52 (C-5), 36.89 (C-6), 39.01 (C-4), 52.61 (OCH_3), 110.60 (C-2), 113.76 (2-CN), 124.52 (C-8), 131.50 (C-9), 161.62 (C-1), 162.58 (C-3); MS *m*/*z* 235 (11, M^+), 220 (8, M – CH_3). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.46; H, 9.02; N, 5.93.

(6*R*)-3-Acetyl-6,10-dimethylundeca-3,9-dien-2-one (9f). Reaction of **7f** with **8** according to general procedure II yielded after chromatography (petroleum ether/acetone, 95:5) 2.05 g (87%) of a sensitive oil: R_f 0.43 (ether/hexane, 1:1); GLC *t*(**9f**)

16.31 min (column 3; 50 °C, 10 °C/min), one signal for **9f** and **11**; HPLC t(**9f**) 4.82 min (column 2; ether/hexane, 1:2; flow 1.5 mL/min); $[\alpha]^{20}_D$ −10.7° (c = 1, CH_3CN); IR (film, cm^{-1}) 1705, 1665, 1630; UV 222 (4.17); ^1H NMR (100 MHz, C_6D_6) δ 0.66–2.28 (m, 7 H, 5-H_2, 6-H, 7-H_2, 8-H_2), 0.77 (d, J = 6.5 Hz, 3 H, 6-CH_3), 1.58 (s br, 3 H, 11-H_3), 1.70 (m, 3 H, 10-CH_3), 1.85 (s, 3 H, CH_3CO), 2.20 (s, 3 H, CH_3CO), 5.16 (mc, 1 H, 9-H), 6.21 (t, J = 8 Hz, 1 H, 4-H); ^{13}C NMR (50 MHz, C_6D_6) δ 17.67 (C-11), 19.63 (6-CH_3), 25.68, 25.80 (10-CH_3 and 3-$COCH_3$), 25.78 (C-8), 31.42 (C-1), 32.83 (C-6), 36.73 and 37.08 (C-5 and C-7), 124.79 (C-9), 131.22 (C-10), 145.08 (C-4), 146.25 (C-3), 196.32 (3-CO), 201.97 (C-2); MS m/z 236 (10, M^+), 221 (6, M − CH_3). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.31; H, 10.37.

(6*R*)-3-[(*Z*)-1-Hydroxyethylidene]-(*E*)-6,10-dimethylundeca-4,9-dien-2-one (11). A solution of **9f** (2.36 g, 10.0 mmol) in chloroform (10 mL) was stirred for 45 days at room temperature. The reaction mixture was evaporated in vacuo. The yield after chromatography (petroleum ether/acetone, 95:5) was 0.47 g (20%) of **9f** and 1.63 g (69%) of **11**: R_f 0.63 (ether/hexane, 1:1); GLC t(**11**) 16.39 min (column 3; 50 °C, 10 °C/min), one signal for **9f** and **11**; IR (film, cm^{-1}) 2200–3600, 1705, 1600; UV 223 (3.88), 290.5 (3.78); ^1H NMR (60 MHz, CCl_4) δ 0.66–2.40 (m, 5 H, 6-H, 7-H_2, 8-H_2), 1.03 (d, J = 6.5 Hz, 3 H, 6-CH_3), 1.57 (s br, 3 H, 11-H_3), 1.67 (s br, 3 H, 10-CH_3), 2.03 (s, 6 H, 1-H_3, 1′-H_3), 5.05 (mc, 1 H, 9-H), 5.31 (dd, J = 16, 7.5 Hz, 1 H, 5-H), 5.93 (d, J = 16 Hz, 1 H, 4-H), 16.42 (s, 1 H, OH, D_2O exchange); ^{13}C NMR (50 MHz, C_6D_6) δ 17.82 (C-11), 20.88 (6-CH_3), 23.87 (C-1 and 3 C-β), 25.92 (10-CH_3), 26.49 (C-8), 37.35 (C-7), 37.44 (C-6), 111.60 (C-3), 122.59 (C-4), 125.00 (C-9), 131.38 (C-10), 142.59 (C-5), 190.74 (C-2 and 3 C-α); MS m/z 236 (12, M^+), 221 (2, M − CH_3). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.17; H, 10.13.

Condensation of 7g with 8. Reaction of **7g** with **8** according to general procedure II yielded **9g** and **9h** in a ratio of 35:65 (^1H NMR). The mixture could be separated by column chromatography (petroleum ether/acetone, 98:2).

Fraction 1. Methyl (*E*)-(5*R*)-2-acetyl-5,9-dimethyldeca-2,8-dienoate (9g): 0.64 g (25%); R_f 0.56 (ether/hexane, 1:1); $[\alpha]^{20}_D$ −13.4° (c = 1, CH_3CN); IR (film, cm^{-1}) 3020, 1730, 1707, 1630, 1290, 1250, 1060; UV sh 213 (3.92); ^1H NMR (100 MHz, C_6D_6) δ 0.60–2.32 (m, 7 H, 4-H_2, 5-H, 6-H_2, 7-H_2), 0.76 (d, J = 6.5 Hz, 3 H, 5-CH_3), 1.56 (s br, 3 H, 10-H_3), 1.68 (m, 3 H, 9-CH_3), 2.22 (s, 3 H, CH_3CO), 3.34 (s, 3 H, OCH_3), 5.11 (tm, J = 7 Hz, 1 H, 8-H), 6.94 (t, J = 8 Hz, 1 H, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ 17.66 (C-10), 19.60 (5-CH_3), 25.80 (C-7), 25.80 (9-CH_3), 30.89 ($COCH_3$), 32.82 (C-5), 36.54 and 37.02 (C-4 and C-6), 51.64 (OCH_3), 124.84 (C-8), 131.23 (C-9), 136.63 (C-2), 147.73 (C-3), 164.83 (C-1), 199.62 (2-CO); MS m/z 252 (18, M^+), 234 (4, M − H_2O). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.73.

Fraction 2. Methyl (*Z*)-(5*R*)-2-acetyl-5,9-dimethyldeca-2,8-dienoate (9h): 1.04 g (41%); R_f 0.49 (ether/hexane, 1:1); $[\alpha]^{20}_D$ −16.1° (c = 1, CH_3CN); IR (film, cm^{-1}) 1735, 1700, 1675, 1635, 1620, 1290, 1050, 1025; UV 222 (4.04); ^1H NMR (100 MHz, C_6D_6) δ 0.67–2.33 (m, 7 H, 4-H_2, 5-H, 6-H_2, 7-H_2), 0.79 (d, J = 6.5 Hz, 3 H, 5-CH_3), 1.55 (s br, 3 H, 10-H_3), 1.67 (m, 3 H, 9-CH_3), 1.96 (s, 3 H, CH_3CO), 3.46 (s, 3 H, OCH_3), 5.13 (tsept, J = 7, 1.5 Hz, 1 H, 8-H), 6.62 (t, J = 8 Hz, 1 H, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ 17.63 (C-10), 19.63 (5-CH_3), 25.78 (C-7), 25.78 (9-CH_3), 26.58 ($COCH_3$), 32.75 (C-5), 37.11 and 37.18 (C-4 and C-6), 51.53 (OCH_3), 124.81 (C-8), 131.21 (C-9), 138.27 (C-2), 146.87 (C-3), 166.83 (C-1), 193.89 (2-CO); MS m/z 252 (12, M^+), 234 (3, M − H_2O). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.60.

Ene Reactions. General Procedure III. Anhydrous zinc bromide (11.0 mmol) was placed under argon in a flame-dried and argon-flushed reaction flask. Anhydrous solvent (25 mL) was added and then the 1,7-diene **9** (10.0 mmol) was added dropwise into the stirred suspension. After being stirred at room temperature for the time given, the reaction mixture was evaporated in vacuo and diluted with ether (40 mL) and water (10 mL). The organic phases were washed with water (2 × 10 mL) and the combined aqueous layers were extracted with ether (2 × 20 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (10 mL) and brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue purified by column chromatography.

General Procedure IV. The alkylidene compounds **9** (10.0 mmol) were dissolved in o-dichlorobenzene (10 mL and refluxed. The solvent was removed in vacuo and the residue purified by column chromatography.

Lewis Acid Catalyzed Cyclization of 9a. Dimethyl (1′*R*,2′*R*,5′*R*)-2-(2′-Isopropenyl-5′-methylcyclohex-1′-yl)-propane-1,3-dioate (15a). Reaction of **9a** according to general procedure III in methylene chloride during 15–30 min yielded after chromatography (ether/petroleum ether, 1:4) 2.30 g (86%) of **15a** as a colorless liquid: R_f 0.56 (ether/hexane, 1:1); GLC t(**15a**) 16.88 min, t(**16a**) 17.11 min (column 1; 100 °C, 5 °C/min), **15a**/**16a** = 96.57:3.43 ± 0.17; bp 128–129 °C/0.5 mbar; $[\alpha]^{20}_D$ −31.5° (c = 1, CH_3CN); IR (film, cm^{-1}) 3065, 1750, 1735, 1645, 1155, 1035, 1020, 895; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 0.95 (dq, J = 3.5, 12 Hz, 1 H, 4′-H ax), 1.11 (q, J = 11.5 Hz, 1 H, 6′-H ax), 1.24–1.57 (m, 2 H, 3′-H ax, 5′-H ax), 1.65 (mc 3 H, 2″-CH_3), 1.57–1.94 (m, 3 H, 3′-H eq, 4′-H eq, 6′-H eq), 2.05 (dt, J = 3.0, 11.5 Hz, 1 H, 2′-H), 2.13 (tt, J = 3.5, 11.5 Hz, 1 H, 1′-H), 3.56 (d, J = 3.5 Hz), 1 H, 2-H)), 3.73 (s, 6 H, OCH_3), 4.74 (mc, 1 H, 1″-H), 4.79 (m, 1 H, 1″-H); double resonance experiment, irradiation at δ 2.13 (1′-H_2), 3.56 (2-H), 4.80 (1″-H_2); significant change at δ 3.56 (s, 2-H) and 1.11 (t, 6′-H ax), 2.13 (1′-H), 1.65 (d, 2″-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) of **15a**/**16a** δ 18.96/19.36 (C-3″), 22.54/17.89 (5′-CH_3), 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 (OCH_3), 53.22/53.14 (C-2), 112.43/112.22 (C-1″), 147.52 (C-2″), 169.03 and 170.11/169.95 (C-1 and C-3); MS m/z 268 (4, M^+), 136 (100, $C_{10}H_{16}$). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.22; H, 9.07. Isomerization: the mixture of **15a** and **16a** did not isomerize under reaction conditions (GLC).

Thermal Cyclization of 9a. Reaction of **9a** according to general procedure IV during 7 h yielded after chromatography (ether/petroleum ether, 1:4) 2.02 g (75%) of a mixture of **15a** and **16a**; **15a** was obtained pure by repeated column chromatography. GLC: **15a**/**16a** = 89.70:10.30 ± 0.12. Isomerization: the mixture of **15a** and **16a** did not isomerize under reaction conditions (GLC).

Lewis Acid Catalyzed Cyclization of 9b. Diethyl (1′*R*,2′*R*,5′*R*)-2-(2′-Isopropenyl-5′-methylcyclohex-1′-yl)-propane-1,3-dioate (15b). Reaction of **9b** according to general procedure III in methylene chloride during 15–30 min yielded after chromatography (ether/petroleum ether, 1:19) 2.46 g (83%) of **15b** as a colorless liquid: R_f 0.59 (ether/hexane, 1:1); GLC t(**15b**) 27.71 min, t(**16b**) 28.08 min (column 2; 50 °C, 5 °C/min), **15b**/**16b** = 96.94:3.06 ± 0.06; $[\alpha]^{20}_D$ −27.7° (c = 1, CH_3CN); IR (film, cm^{-1}), 3065, 1750, 1735, 1645, 1155, 1035, 895; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 0.94–1.88 (m, 7 H, 3′-H_2, 4′-H_2, 5′-H, 6′-H_2), 1.26 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.66 (s br, 3 H, 2″-CH_3), 1.94–2.22 (m, 2 H, 1′-H, 2′-H), 3.51 (d, J = 3 Hz, 1 H, 2-H), 4.17 (q, J = 7 Hz, 2 H, OCH_2CH_3), 4.21 (q, J = 7 Hz, 2 H, OCH_2CH_3), 4.77 (m, 1 H, 1″-H), 4.80 (m, 1 H, 1″-H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 14.17 and 14.25 (OCH_2CH_3), 18.97 (C-3″), 22.69 (5′-CH_3), 32.60 (C-3′), 32.97 (C-5′), 35.03 (C-4′), 36.71 (C-6′), 40.00 (C-1′), 48.76 (C-2′), 53.21 (C-2), 60.46 and 60.82 (OCH_2CH_3), 112.53 (C-1″), 147.63 (C-2″), 168.17 and 169.32 (C-1 and C-3); MS m/z 296 (18, M^+), 251 (15, M − C_2H_5O), 136 (100, $C_{10}H_{16}$). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.96; H, 9.40.

Lewis Acid Catalyzed Cyclization of 9c. Dibenzyl (1′*R*,2′*R*,5′*R*)-2-(2′-Isopropenyl-5′-methylcyclohex-1′-yl)-propane-1,3-dioate (15c). Reaction of **9c** according to general procedure III in methylene chloride during 45–60 min yielded after chromatography (ether/petroleum ether, 1:9) 3.32 g (79%) of **15c** as a colorless oil: R_f 0.31 (ether/petroleum ether, 1:9); GLC t(**15c**) 23.27 min, t(**16c**) 23.93 min (column 2; 200 °C, 3 °C/min), **15c**/**16c** = 97.48:2.52 ± 0.095; $[\alpha]^{20}_D$ −21.4° (c = 1, CH_3CN); IR (film, cm^{-1}) 3070, 3030, 1750, 1735, 1645, 1610, 1585, 1495, 1215, 1155, 900, 740, 695; UV sh 212 (4.26), 257 (2.81); ^1H NMR (200 MHz, $CDCl_3$) δ 0.81 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 0.74–1.80 (m, 7 H, 3′-H_2, 4′-H_2, 5′-H, 6′-H_2), 1.59 (m, 3 H, 2″-CH_3), 2.03 (dt, J = 3.5, 11.5 Hz, 1 H, 2′-H), 2.12 (tt, J = 11.5, 3.5 Hz, 1 H, 1′-H), 3.61 (d, J = 3.5 Hz, 1 H, 2-H), 4.65 (m, 1 H, 1″-H), 4.7 (m, 1 H, 1″-H), 5.14 (mc, 4 H, OCH_2), 7.34 (s br, 10 H, phenyl); ^{13}C NMR (20 MHz, $CDCl_3$) δ 18.77 (C-3″), 22.42 (5′-CH_3), 32.19 (C-3′), 32.60 (C-5′), 34.57 (C-4′), 36.39 (C-6′), 39.97 (C-1′), 48.47 (C-2′), 53.21 (C-2), 66.44 and 66.64 (OCH_2), 112.58 (C-1″), 128.07, 128.16, 128.38 and 128.47 (CH-arom.), 135.62 (C-arom.), 147.26 (C-2″), 168.05 and 169.21 (C-1 and C-3); MS m/z 420 (M^+), 329 (22, M − C_7H_7), 283 (29, $C_7H_{15}O_4$),

91 (100, C_7H_7). Anal. Calcd for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 77.15; H, 7.64.

Thermal Cyclization of 9c. Reaction of **9c** according to general procedure IV during 8 h yielded after chromatography (ether/petroleum ether, 1:9) 2.77 g (66%) of a mixture of **15c** and **16c**. GLC: **15c/16c** = 91.50:8.50 ± 0.23.

I. Lewis Acid Catalyzed Cyclization of 9d. (1′*R*,2′*R*,5′*R*)-2-(2′-Isopropenyl-5′-methylcyclohex-1′-yl)-propane-1,3-dinitrile (15d). Reaction of **9d** according to general procedure III in benzene within 1.5–1.75 h yielded after chromatography (ether/petroleum ether, 1:9) 1.78 g (88%) of **15d**: R_f 0.10 (ether/hexane, 1:9); GLC t(**15d**) 5.18 min, t(**16d**) 5.30 min (column 1; 100 °C, 4 °C/min), **15d/16d** = 94.24:5.76 ± 0.12; mp 30–33 °C (petroleum ether); $[\alpha]^{20}_D$ −35.9° (c = 1, CH_3CN); IR (KBr, cm^{-1}) 3070, 2250, 1645, 905, 735; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82–1.87 (m, 6 H), 1.00 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 1.68 (t, J = 1 Hz, 3 H, 2″-CH_3), 1.99 (tt, J = 11, 3 Hz, 1 H, 1′-H), 1.99–2.19 (m, 2 H, among others 2′-H), 3.90 (d, J = 3 Hz, 1 H, 2-H), 4.93 (mc, 2 H, 1″-H_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.56 (C-3″), 22.12 (5′-CH_3), 27.00 (C-2), 30.95 (C-3′), 32.00 (C-5′), 33.93 (C-4′), 36.56 (C-6′), 40.57 (C-1′), 48.41 (C-2′), 111.41 and 112.98 (C-1 and C-2), 114.24 (C-1″), 145.02 (C-2″); MS m/z 202 (10, M$^+$), 187 (9, M − CH_3), 137 (36, $C_{10}H_{17}$), 41 (100, C_3H_5). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.37; H, 9.02; N, 13.71.

II. Lewis Acid Catalyzed Cyclization of 9d. Reaction of **9d** according to general procedure III in benzene during 24 h after chromatography (ether/petroleum ether, 1:9) afforded two fractions.

Fraction 1. (1*R*,4*R*,6*R*)-4,8,8-Trimethylbicyclo[4.2.0]octane-7,7-dicarbonitrile (25): 0.73 g (36%); R_f 0.17 (ether/hexane, 1:9); GLC t(**25**) 14.02 min, t(**26**) 14.16 min (column 1; 50 °C, 3 °C/min); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92–2.00 (m, 8 H), 0.98 (d, J = 6.5 Hz, 3 H, 4-CH_3), 1.37 (s, 6 H, 8-CH_3), 2.29 (ddd, J = 12.5, 11.5, 3.5 Hz, 1 H, 1-H, or 6-H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 18.91 (8-CH_3), 22.40 (4-CH_3), 25.66 (C-2), 25.90 (8-CH_3), 32.55 (C-4), 34.01 and 35.66 (C-3 and C-5), 40.57 (C-7 or C-8), 46.03 and 50.02 (C-1 and C-6), 51.55 (C-7 or C-8), 113.60 and 113.87 (CN), **25/26** = 96:4; MS m/z 202 (6, M$^+$), 187 (35, M − CH_3), 41 (100, C_3H_5). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.18; H, 9.08; N, 13.73.

Fraction 2: 0.99 g (49%) of a mixture of **15d** and **16d**.

Thermal Cyclization of 9d. Reaction of **9d** according to general procedure IV during 1 h yielded after chromatography (ether/petroleum ether, 1:9) 1.81 g (90%) of a mixture of **15d**, **16d**, and **24**. GLC: **15d** + **16d**/**24** = 92.43:7.57 ± 0.24. ^{13}C NMR: **15d/16d** = 87:13.

Lewis Acid Catalyzed Cyclization of 9e. Reaction of **9e** according to general procedure III in benzene during 1 h after chromatography (ether/petroleum ether, 1:4) afforded three fractions.

Fraction 1. Mixture (0.45 g (19%)) of Methyl (2*R*,1′*R*,2′*R*,5′*R*)- and (2*S*,1′*S*,2′*S*,5′*S*)-2-(2′-Isopropenyl-5′-methylcyclohex-1′-yl)cyanoacetate ((2*R*)-15e), (2*S*)-15e, and 16e. From the mixture of diastereomers (2*R*)-**15e** was obtained as a racemate by crystallization from hexane: R_f 0.55 (ether/hexane, 1:1); mp 89–90 °C (hexane); GLC, the analysis of the product mixture was performed after demethoxycarbonylation,[17] which yielded a mixture of **27** and **28**; a control experiment was run with diastereomerically pure (2*R*)-**15e**; t(**27**) 10.36 min, t(**28**) 10.55 min (column 1; 50 °C, 3 °C/min), **27/28** = 96.31:3.69 ± 0.20; IR (KBr, cm^{-1}) 3070, 2250, 1755, 1745, 1645, 1280, 1235, 1205, 895; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 0.98–1.84 (m, 7 H), 1.69 (mc, 3 H, 2″-CH_3), 2.08 (dt, J = 3.5, 11.5 Hz, 1 H, 2′-H), 2.16 (tt, J = 3.5, 11.5 Hz, 1 H, 1′-H), 3.73 (d, J = 3 Hz, 1 H, 2-H), 3.84 (s, 3 H, OCH_3), 4.79–4.98 (m, 2 H, 1″-H_2); ^{13}C NMR (20 MHz, $CDCl_3$) δ 18.61 (C-3″), 22.32 (5′-CH_3), 31.38 (C-3′), 32.11 (C-5′), 34.30 (C-4′), 36.42 (C-6′), 40.04 and 41.63 (C-2 and C-1′), 48.72 (C-2′), 53.25 (OCH_3), 113.42 and 114.97 (C-3 and C-1″), 146.13 (C-2″), 166.94 (C-1); (2*R*)-**15e**/(2*S*)-**15e** = 87:13; MS m/z 235 (24, M$^+$), 220 (10, M − CH_3), 176 (89, M − $C_2H_3O_2$), 137 (100, $C_{10}H_{17}$). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.64; H, 9.22; N, 5.98.

Fraction 2. (4a*R*,6*R*,8a*R*)-4-Cyano-3-methoxy-1,1,6-trimethyl-4a,5,6,7,8,8a-hexahydro-1*H*-2-benzopyran (17a): 1.60 g (68%); R_f 0.42 (ether/hexane, 1:1); $[\alpha]^{20}_D$ −19.9° (c = 1, CH_3CN); IR (film, cm^{-1}) 2200, 1625, 1155, 1135, 1095; UV 237 (4.06); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (q, J = 12 Hz, 1 H, 5-H ax), 0.88–1.92 (m, 6 H), 0.94 (d, J = 6.5 Hz, 3 H, 6-CH_3), 1.17 (s, 3 H, 1-CH_3 ax), 1.38 (s, 3 H, 1-CH_3 eq), 2.00 (ddd, J = 12, 10.5, 3 Hz, 1 H, H-4a or H-8a), 2.16 (dm, J = 12 Hz, 1 H, 5-H eq); ^{13}C NMR (20 MHz, $CDCl_3$) δ 20.10 (1-CH_3 ax), 22.11 (6-CH_3), 26.74 (C-8), 26.84 (1-CH_3 eq), 31.83 (C-6), 33.69 (C-4a), 34.83 (C-7), 39.83 (C-5), 47.21 (C-8a), 54.44 (OCH_3), 62.38 (C-1), 84.77 (C-4), 118.34 (CN), 164.57 (C-3), **17a/18a** = 91:9; MS m/z 235 (38, M$^+$), 220 (18, M − CH_3), 192 (43, M − C_3H_7), 41 (100, C_3H_5). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.41; H, 8.96; N, 5.97.

Fraction 3. (4*R*,4a*R*,6*R*,8a*R*)-4-Cyano-1,1,6-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-1*H*-2-benzopyran-3-one (33): 0.07–0.19 g (3–8%); R_f 0.26 (ether/hexane, 1:1); mp 124–127 °C (methanol), 136–138 °C (benzene); $[\alpha]^{20}_D$ −44.3° (c = 1, CH_3CN); IR (KBr, cm^{-1}) 2250, 1710, 1140, 1110, 1100; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79 (q, J = 12 Hz, 1 H, 5-H ax), 0.91–1.69 (m, 4 H), 0.97 (d, J = 6.5 Hz, 3 H, 6-CH_3), 1.34 (s, 3 H, 1-CH_3 ax), 1.45 (s, 3 H, 1-CH_3 eq), 1.73–1.94 (m, 2 H), 2.10 (dq, J = 3.5, 11.5 Hz, 1 H, 4a-H), 2.17–2.33 (m, 1 H, 5-H eq), 3.21 (d, J = 12 Hz, 0.9 H, 4-H ax), 3.65 (d, J = 6 Hz, 0.1 H, 4-H eq); ^{13}C NMR (20 MHz, $CDCl_3$) δ 21.91 and 23.40 (1-CH_3 ax and 6-CH_3), 27.01 (C-8), 28.00 (1-CH_3 eq), 31.31 (C-6), 33.80 (C-7), 36.52 (C-4a), 39.84 (C-5), 40.72 (C-4), 45.79 (C-8a), 88.01 (C-1), 115.89 (CN), 163.26 (C-3), **33/34** = 89:11; MS m/z 206 (10, M − CH_3), 162 (24, M − C_3H_7O), 134 (43, 162 − CO), 43 (100, C_3H_5). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.52; H, 8.63; N, 6.34.

Thermal Cyclization of 9e. Reaction of **9e** according to general procedure IV during 2.5 h yielded after chromatography (ether/petroleum ether, 1:4) 2.09 g (89%) of a mixture of (2*R*)-**15e**, (2*S*)-**15e**, and **16e**. GLC: **27/28** = 88.3:11.7 ± 0.1. ^{13}C NMR: (2*R*)-**15e**/(2*S*)-15e = 88:12.

Lewis Acid Catalyzed Cyclization of 9f. Reaction of **9f** according to general procedure III in benzene during 30 min after chromatography (ether/petroleum ether, 1:4) afforded two fractions.

Fraction 1. (4a*R*,6*R*,8a*R*)-4-Acetyl-1,1,3,6-tetramethyl-4a,5,6,7,8,8a-hexahydro-1*H*-2-benzopyran (17b): 2.03 g (86%); R_f 0.44 (ether/hexane, 1:1); HPLC t(**17b**) 4.12 min, t(**18b**) 4.92 min (column 2; ether/hexane, 1:4); flow 2.0 mL/min), **17b/18b** = 94.55:5.45 ± 0.16; mp 65–66 °C (petroleum ether); $[\alpha]^{20}_D$ −4.4° (c = 1, CH_3CN); IR (KBr, cm^{-1}), 1675, 1600, 1130; UV 264 (3.87); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.68 (q, J = 11.5 Hz, 1 H, 5-H ax), 0.84–2.02 (m, 7 H), 0.89 (d, J = 6.5 Hz, 3 H, 6-CH_3), 1.08 (s, 3 H, 1-CH_3 ax), 1.29 (s, 3 H, 1-CH_3 eq), 1.97 (d, J = 1.5 Hz, 3 H, 3-CH_3), 2.14 (dm, J = 11.5 Hz, 1 H, 5-H eq), 2.22 (s, 3 H, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.44 and 19.71 (1-CH_3 ax and 3-CH_3), 22.36 (6-CH_3), 27.28 (1-CH_3 eq), 27.35 (C-8), 30.39 (CO-CH_3), 32.37 (C-6), 35.08 (C-7), 35.93 (C-4a), 40.05 (C-5), 47.87 (C-8a), 77.99 (C-1), 115.70 (C-4), 155.25 (C-3), 201.76 (CO); MS m/z 236 (16, M$^+$), 221 (12, M − CH_3), 203 (11, M − CH_3 + H_2O). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.29; H, 10.32.

Fraction 2. (1*R*,4*R*,5*S*,6*R*,8*R*)-5-Acetyl-4-hydroxy-4,8-dimethyl-2-methylenebicyclo[4.4.0]decane (19a): 0.17 g (7%); R_f 0.34 (ether/hexane, 1:1); mp 72–74 °C (petroleum ether); IR (KBr, cm^{-1}) 3490, 3080, 1690, 1645,1165, 890; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70–2.00 (m, 9 H), 0.87 (d, J = 6.5 Hz, 3 H, 8-CH_3), 1.18 (s, 3 H, 4-CH_3 eq), 2.14 (dm, J = 14 Hz, 1 H, 3-H ax), 2.28 (s, 3 H, CH_3CO), 2.33 (d, J = 14 Hz, 1 H, 3-H eq), 2.48 (d, J = 11 Hz, 1 H, 5-H ax), 3.17 (s br, 1 H, OH), 4.81 (mc, 2 H, methylene-H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 22.44 (8-CH_3), 28.19 (C-10), 28.59 (4-CH_3), 32.22 (C-8), 33.38 ($COCH_3$), 34.45 (C-9), 40.40 (C-7), 41.99 and 45.25 (C-1 and C-6), 49.51 (C-3), 64.78 (C-5), 70.95 (C-4), 108.45 (CH_2═), 147.27 (C-2), 215.08 (CO); MS m/z 236 (6, M$^+$), 218 (19, M − H_2O), 203 (3, 218 − CH_3). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.11; H, 10.29.

Thermal Cyclization of 9f. Reaction of **9f** according to general procedure IV during 1 h after chromatography (ether/petroleum ether, 1:4) afforded two fractions.

Fraction 1: 1.91 g (81%) of a mixture of **17b**, **18b**, and **15f**. ^{13}C NMR: **17b/18b/15f** = 85:10:5, **17b/18b** = 89:11.

Fraction 2: 0.21 g (9%) of a mixture of **19a** and **20a**. ^{13}C NMR: **19a/20a** = 91:9.

Lewis Acid Cyclization of 9g and 9h. Reaction of a mixture of **9g** and **9h** according to general procedure III in methylene chloride during 30 min after chromatography (ether/petroleum ether, 1:9) afforded four fractions.

Fraction 1. (4a*R*,6*R*,8a*R*)-4-(Methoxycarbonyl)-1,1,3,6-tetramethyl-4a,5,6,7,8,8a-hexahydro-1*H*-2-benzopyran (17c): 0.45 g (18%); R_f 0.56 (ether/hexane, 1:1); mp 53–55 °C (petroleum ether); $[\alpha]^{20}_D$ −89.9° (c = 1, CH_3CN); IR (KBr, cm^{-1}) 1710, 1620, 1130, 1115, 1065, 1005, 780; UV 245 (3.91); ^1H NMR (200 MHz, $CDCl_3$) δ 0.60 (q, J = 12.5 Hz, 1 H, 5-H ax), 0.85–2.17 (m, 8 H), 0.89 (d, J = 6.5 Hz, 3 H, 6-CH_3), 1.06 (s, 3 H, 1-CH_3 ax), 1.28 (s, 3 H, 1-CH_3 eq), 2.08 (m, 3 H, 3-CH_3), 3.72 (s, 3 H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.39 and 19.97 (1-CH_3 ax and 3-CH_3), 22.44 (6-CH_3), 27.26 (1-CH_3 eq), 27.39 (C-8), 32.33 (C-6), 35.29 (C-7), 35.40 (C-4a), 39.68 (C-5), 47.95 (C-8a), 50.53 (OCH_3), 78.18 (C-1), 105.43 (C-4), 159.02 (C-3), 168.99 (CO), **17c/18c** = 96:4; MS m/z 252 (30, M^+), 237 (3, M − CH_3), 234 (3, M − H_2O), 136 (56, $C_{10}H_{16}$), 121 (27, 136 − CH_3), 43 (100, C_3H_7). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.37; H, 9.63.

Fraction 2. Methyl (1′*R*,2′*R*,5′*R*)-2-(2′-isopropenyl-5′-methylcyclohex-1′-yl)acetoacetate (15g) as a mixture (0.23 g (9%) cf epimers at C-2: R_f 0.47 (ether/hexane, 1:1); IR (film, cm^{-1}) 3070, 1735, 1715, 1645, 1200, 1160, 895; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83–2.28 (m, 9 H), 0.88 (d, J = 6.5 Hz, 3 H, 5′-CH_3), 1.61 (mc, ≈1 H, 2″-CH_3), 1.64 (mc, ≈2 H, 2″-CH_3), 2.18 (s, 3 H, CH_3CO), 3.56 (mc, 1 H, 2-H), 3.69 (s, 2.1 H, OCH_3), 3.72 (s, 0.9 H, OCH_3), 4.69–4.81 (mc, 2 H, 1″-H_2); ^{13}C NMR (20 MHz, $CDCl_3$) δ 18.43/18.95 (C-3″) 22.50 (5′-CH_3), 31.38/29.50 (CH_3CO), 32.25 (C-3′), 32.86/32.72 (C-5′), 34.63/34.69 (C-4′), 36.99/36.73 (C-6′), 40.43/38.88 (C-1′), 49.41/49.19 (C-2′), 52.05/51.75 (OCH_3), 60.72/61.25 (C-2), 112.69/112.48 (C-1″), 147.97/147.71 (C-2″), 170.75/169.85 (C-1), 203.75/203.06 (C-3); ratio 70:30; MS m/z 252 (7, M^+), 234 (12, M − H_2O), 220 (5, M − CH_3OH), 136 (87, $C_{10}H_{16}$). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.63.

Fraction 3. Methyl (1*R*,4*R*,5*S*,6*R*,8*R*)-4-hydroxy-4,8-dimethyl-2-methylenebicyclo[4.4.0]decane-5-carboxylate (19b): 1.13 g (45%); R_f 0.28 (ether/hexane, 1:1); mp 132–133 °C (ether/petroleum ether, 1:1); $[\alpha]^{20}_D$ −4.8° (c = 1, CH_3CN); IR (KBr, cm^{-1}) 3510, 3090, 1705, 1650, 1180, 892; ^1H NMR (200 MHz, $CDCl_3$) δ 0.80 (q, J = 12.5 Hz, 1 H, 7-H ax), 0.85–1.08 (m, 1 H), 0.88 (d, J = 6.5 Hz, 8-CH_3), 1.20 (s, 8 H, 4-CH_3 eq), 1.26–2.00 (m, 7 H), 2.12 (dm, J = 13.5 Hz, 1 H, 3-H ax), 2.29 (d, J = 11 Hz, 1 H, 5-H ax), 2.41 (d, J = 13.5 Hz, 1 H, 3-H eq), 3.24 (d, J = 2 Hz; 1 H, OH), 3.77 (s, 3 H, OCH_3), 4.82 (mc, 2 H, methylene-H); double resonance experiments, irradiation at δ 2.12 (3-H ax), 3.24 (OH), 4.82 (methylene-H); significant change at δ 3.24 (s, OH), 4.82 (methylene-H), 2.12 (3-H ax), 2.12 (3-H ax); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.55 (8-CH_3), 28.27 (C-10), 28.93 (4-CH_3), 32.23 (C-8), 34.56 (C-9), 40.49 (C-7), 41.47 and 45.17 (C-1 and C-6), 48.60 (C-3), 51.60 (OCH_3), 58.55 (C-5), 70.74 (C-4), 108.45 (CH_2=), 147.41 (C-2), 176.03 (CO), **19b/20b** = 97:3; MS m/z 252 (45, M^+), 234 (19, M − H_2O), 220 (15, M − CH_3OH). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.67.

Fraction 4. Methyl (4*R*,5*S*,6*R*,8*R*)-4-hydroxy-2,4,8-trimethylbicyclo[4.4.0]dec-1-ene-5-carboxylate (32): 0.50 g (20%); R_f 0.25 (ether/hexane, 1:1); IR (film, cm^{-1}) 3530, 1715, 1170; ^1H NMR (200 MHz, $CDCl_3$) δ 0.73 (q, J = 12 Hz, 1 H, 7-H ax), 0.80–1.90 (m, 5 H), 0.88 (d, J = 6.5 Hz, 3 H, 8-CH_3), 1.20 (s, 3 H, 4-CH_3), 1.65 (s br, 3 H, 2-CH_3), 2.00 (dm, J = 17.5 Hz, 1 H, 3-H), 2.17 (dm, J = 17.5 Hz, 1 H, 3-H), 2.25 (d, J = 10.75 Hz, 1 H, 5-H ax), 2.47 (tm, J = 12 Hz, 1 H), 2.74 (mc, 1 H), 3.02 (d, J = 2 Hz, 1 H, OH), 3.78 (s, 3 H, OCH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 18.32 (2-CH_3), 22.29 (8-CH_3), 28.30 (4-CH_3), 28.30 (C-10), 32.20 (C-8), 35.21 (C-9), 38.33 (C-6), 42.06 (C-7), 45.37 (C-3), 51.45 (OCH_3), 56.65 (C-5), 68.36 (C-4), 121.08 (C-2), 129.50 (C-1), 176.54 (5-CO); MS m/z 252 (1, M^+), 234 (32, M − H_2O), 219 (5, 234 − CH_3), 175 (100, 234 − $C_2H_3O_2$). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.59.

Thermal Cyclization of 9g and 9h. Reaction of a mixture of **9g** and **9h** or of pure **9g** and **9h** according to general procedure IV after chromatography (ether/petroleum ether, 1:9) afforded **17c/18c** and **15g** (Table I and II).

Brønsted Acid Cyclization of 9g/9h. A mixture of **9g/9h** (2.52 g, 10.0 mmol) in methylene chloride (25 mL) was treated with acetic acid (2.75 g, 45.6 mmol) and concentrated hydrochloric acid (1.00 g, 10.0 mmol). The mixture was stirred for 1 h. After removal of the solvent in vacuo, the residue was diluted with ether (25 mL) and water (25 mL). The inorganic phase was extracted with ether (3 × 25 mL). The combined organic phases were washed with saturated hydrogen carbonate solution (25 mL), water (25 mL), and brine (25 mL) and then dried (Na_2SO_4). The solvent was removed and the residue was purified by chromatography (ether/petroleum ether, 1:4) to yield 2.12 g (84%) of a mixture of **17c** and **18c**. ^{13}C NMR: **17c/18c** = 96:4.

Reaction of Citronellal (8) with Cyanoacetic Acid (7i). A mixture of **8** (15.4 g, 0.10 mol) and **7i** (8.50 g, 0.10 mol) was treated with a solution of sodium hydroxide (6.00 g, 0.15 mol) in water (60 mL) at 0 °C. After being stirred for 15 min at 0 °C, the reaction mixture was extracted with ether (2 × 50 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether (3 × 50 mL). The combined etheral phases were washed with brine (2 × 25 mL) and dried (Na_2SO_4). After removal of the solvent, 21.0 g (95%) of the alkylidene compound **9i** was obtained (^1H NMR spectroscopy), which however cyclized at room temperature to give **33** and **34** (^{13}C NMR spectroscopy). After several weeks the crude product crystallized. Recrystallization from methanol or benzene yielded 9.95 g (45%) of **33**: mp 136–138 °C (benzene) (lit.[20] mp 137–138 °C (benzene)).

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