Diastereoselectivity in the Addition of Allylzinc Reagents to δ-Alkoxy-γ,δ-disubstituted Alkenyllithium Compounds

Nicolas Bernard, Fabrice Chemla,* Franck Ferreira, Naouel Mostefai, and Jean-F. Normant[a]

Abstract: The carbometalation reaction of allyl- and crotylzinc bromide with metalated disubstituted homoallylic ethers gives tri- or tetrasubstituted 5-hexenyl ethers with excellent control of the diastereoselectivity. The stereochemistry of this reaction is discussed and has been attributed to an early transition state with chelation to the oxygen atom in the energetically favored conformer as the stereodetermining step.

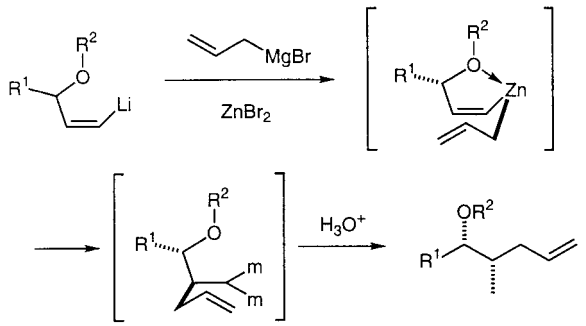
Keywords: carbometalation · conformation analysis · diastereoselectivity · metallacycles · zinc

Introduction

Since its discovery by Gaudemar and co-workers,[1] the addition of allylzinc compounds to vinyl metal compounds, which leads to 1,1-dimetallic species, has been widely studied over the past ten years from both a synthetic[2] and theoretical point of view.[3] The stereoselectivity of this reaction has been studied in detail, particularly in the case of vinyl metal compounds bearing a heteroatom in the allylic position. In this case, the allyl metal reagent reacts with good facial stereoselectivity. This has been attributed to an internal coordination during the addition process, which then occurs *anti* to the substituent in the allylic position (Scheme 1).[4]

In the case of vinyllithium compounds derived from homoallylic ethers, a more complex stereochemical behavior is observed.[5] The reaction occurs with excellent stereocontrol; however, the relative configuration of the newly formed carbon center depends on the substitution of the vinylic partner (Scheme 2).

In the case of the metalated homoallylic ether **1a**, which bears only one substituent, the allyl metal moiety reacts on the less hindered face *anti* to this substituent to give ether **2a** with a high selectivity after hydrolysis. When the metalated homoallylic ether bears a substituent in both the allylic and homoallylic positions, two different cases have been reported.



Scheme 1. Reaction of vinyllithium compounds bearing an alkoxy moiety in the allylic position.

For lithio compound **1b**, both substituents are *cis* to each other and then located on the same face of the presumed six-membered ring induced by the internal coordination ("matched" case). For this compound, the allyl metal reaction takes place in a stereoselective fashion to give ether **2b** as a single diastereomer. The relative configurations have been determined and show that the reaction of the allylzinc moiety takes place on the less hindered face, as in the case of **1a**. In contrast, in the reaction of lithio compound **1c**, in which substituents are *trans* to each other in the six-membered-ring intermediate ("mismatched" case), stereochemical analysis of the resulting ether **2c** shows that the reaction with allylzinc species surprisingly occurs on the same side as the allylic substituent. Thus the stereochemical course of the reaction seems to be controlled only by the homoallylic substituent and to be independent of the substituent in the allylic position. However, the question of the generality of this strange behavior has remained unsolved, because in this preliminary study only one example of each case ("matched" or "mismatched" as defined above) was reported. Moreover, in the

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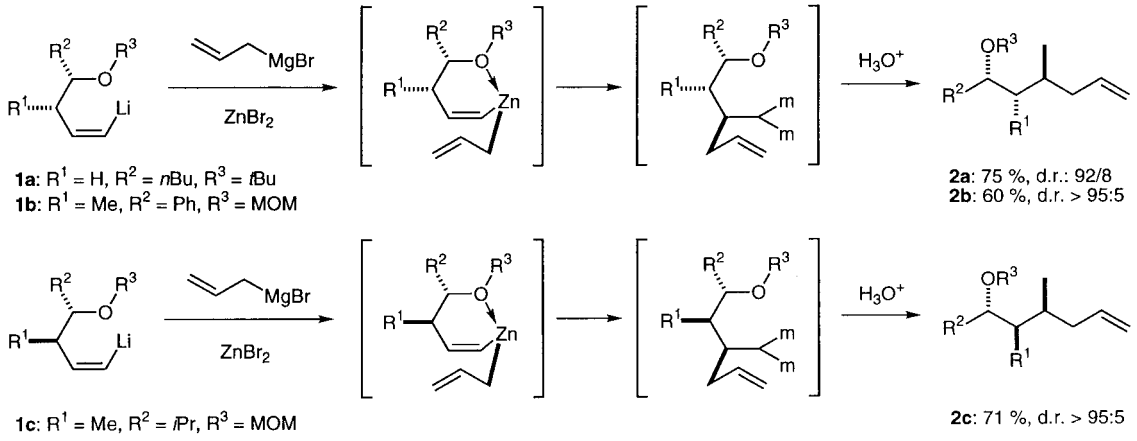


Scheme 2. Reaction of substituted metalated homoallylic ethers.

"mismatched" case, the steric demands of the two substituents were very different, and thus this example was possibly biased. We wanted to examine the scope and the limitations of the stereochemical course of this reaction, and we report here our results in a more general study on the reaction of diversely substituted metalated homoallylic ethers with allyl and crotyl metal compounds.

Results

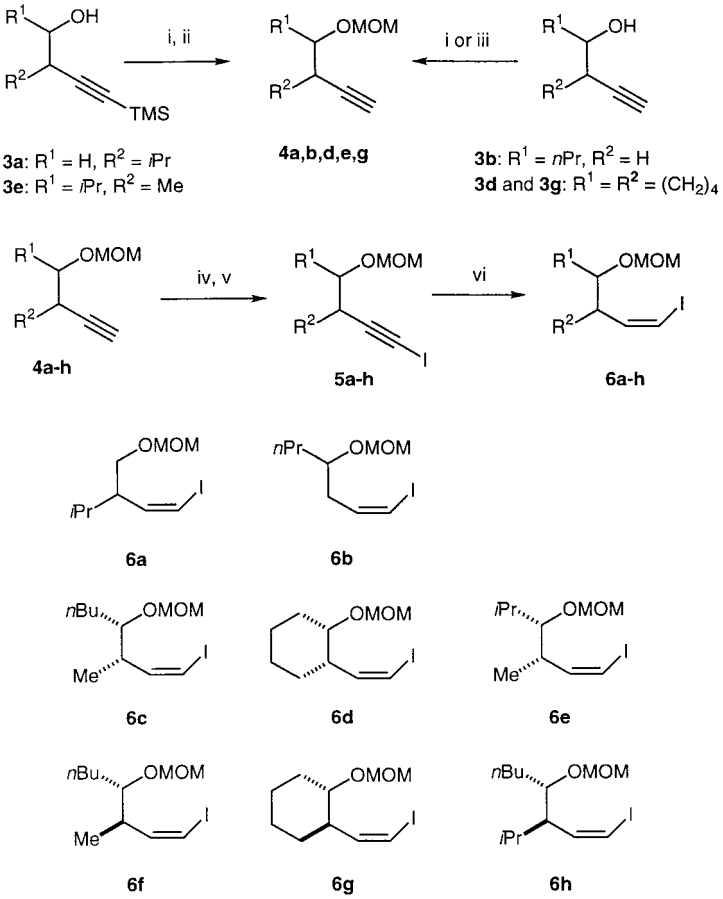
Preparation of the metalated homoallylic ethers: The metalated substituted homoallylic ethers **7a–h** (see Scheme 4) needed for our study were prepared in situ from the corresponding vinyl iodides **6a–h** (see Scheme 3) by Li–I exchange with *t*BuLi (2 equivalents) in diethyl ether. The iodides were prepared from the corresponding substituted homopropargylic alcohols[6, 7, 8] or ethers[6] by the procedures depicted in Scheme 3.

Reaction of metalated homoallylic ethers 7a–h with allylzinc and crotylzinc bromide: The reactions of metalated substituted homoallylic ethers **7a–g** with allylzinc bromide were conducted in diethyl ether at −25 °C within 3–7 h. The yields of the isolated products are reported in Table 1. After

Table 1. Products from carbometalation and iodoetherification reactions.

Entry	Starting vinyl iodide	Carbometalation product	Yield [%]	Iodoetherification product	Yield [%][a]
1	**6a**	**8ax**	74	**10ax**	57
2	**6a**	**8ay**	59	**10ay**	47
3	**6b**	**8b**	85		
4	**6c**	**8cx**	52		
5	**6c**	**8cy**	71	**10cy**	73
6	**6d**	**8d**	51	**10d**	30
7	**6e**	**8e**	72	**10e**	63
8	**6f**	**8fx**	79	**10fx**[b]	76
9	**6f**	**8fy**[c]	65	**10fy**	57
10	**6g**	**8g**[d]	65	**10g**	57
11	**6h**		NR[e]		

[a] Yield over two steps after purification. [b] As a mixture of two diastereomers in a 60/40 ratio. [c] As a mixture of two diastereomers in a 68/32 ratio. [d] As a mixture of two diastereomers in a 90/10 ratio. [e] NR = no reaction.



Scheme 3. Preparation of vinyl iodide precursors. i) MOMCl, iPr_2NEt; ii) KF, DMF:H_2O; iii) $CH_2(OMe)_2$, P_2O_5 or LiBr, PTSA; iv) *n*BuLi, THF; v) I_2; vi) KO_2C-N=N-CO_2K. MOM = methoxymethyl; PTSA = *p*-toluenesulfonic acid.

hydrolysis, the resulting disubstituted ethers **8ax**, **8b** (starting from vinyl iodides **6a**, **6b**, respectively) or trisubstituted ethers **8cx**, **8d**, **8e**, **8fx**, and **8g** (from **6c–g** respectively) were obtained in 51–85% yields (see Scheme 4 and Table 1, entries 1, 3, 4, 6, 7, 8, and 10). No reaction with the metalated homoallylic ether **7h**, derived from **6h**, was observed, even after 20 h, and the ether **9** was isolated upon hydrolysis (Table 1, entry 11). The reactions of metalated substituted

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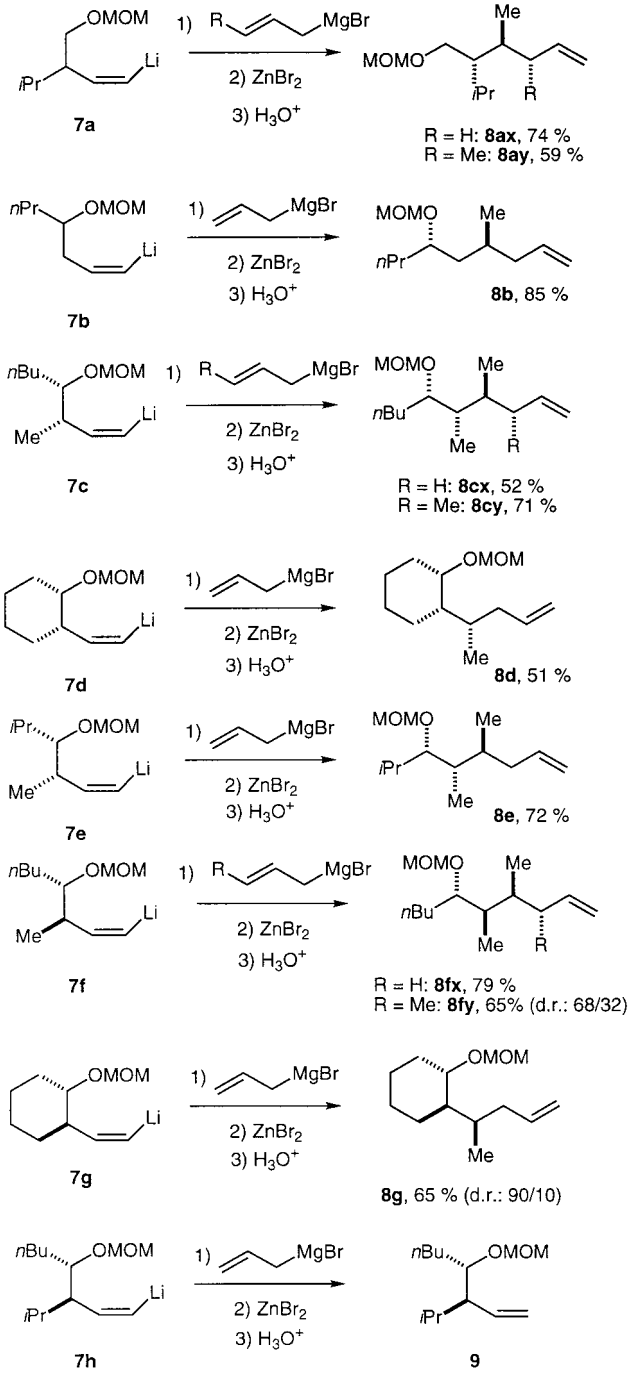
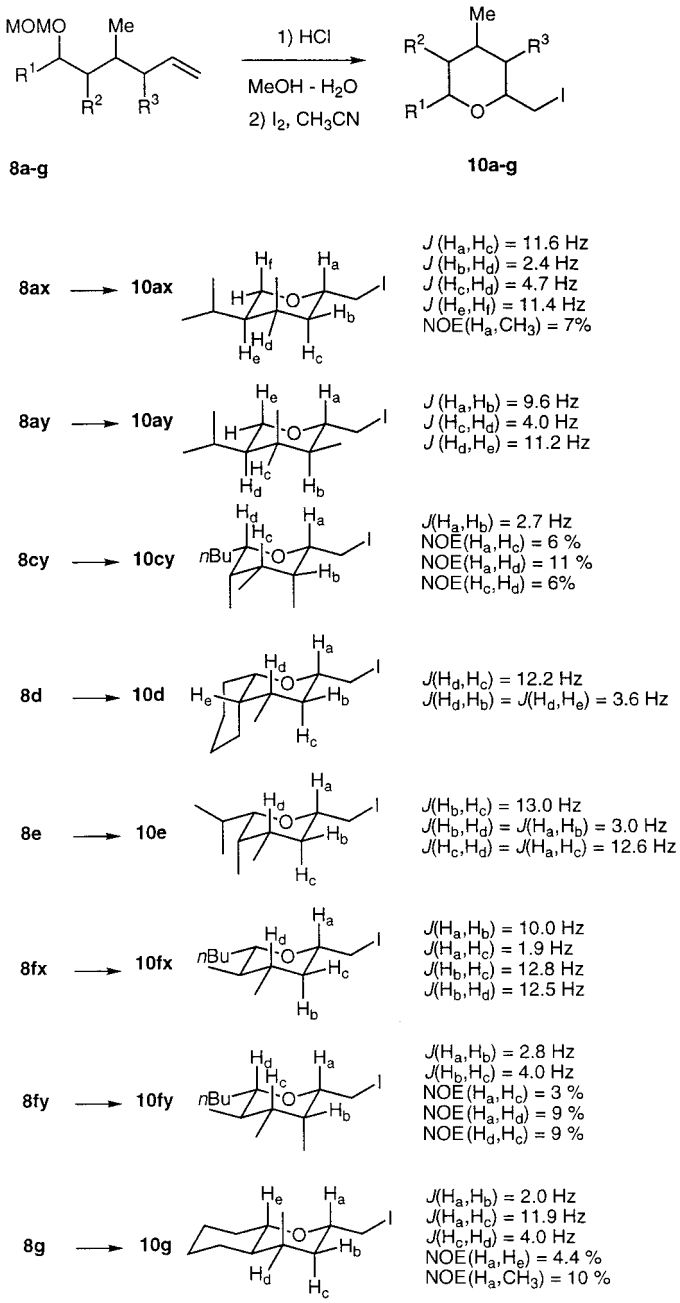


Scheme 4. Reaction of metalated substituted homoallylic ethers with allylzinc and crotylzinc bromide.

homoallylic ethers **7a**, **7c**, and **7f** with crotylzinc bromide were conducted in diethyl ether to give, after hydrolysis, the corresponding ethers **8ay**, **8cy**, and **8fy** in 59, 71, and 65% yield, respectively (Table 1, entries 2, 5, and 9). In all cases, products were obtained as single diastereomers (except for **8fy**, which was obtained as a mixture of two diastereomers in a 68/32 ratio, and **8g**, which was obtained as a mixture of two diastereomers in a 90/10 ratio), based on ^{1}H and ^{13}C NMR analysis. The relative configurations of all stereogenic centers were determined (see below).

Determination of the relative stereochemistry of compounds 8a–g: The relative stereochemistries of compounds **8a–g** were determined by the transformation of these compounds into the substituted iodomethyltetrahydropyrans **10a–g** by use of the general procedure depicted in Scheme 5: hydrolysis



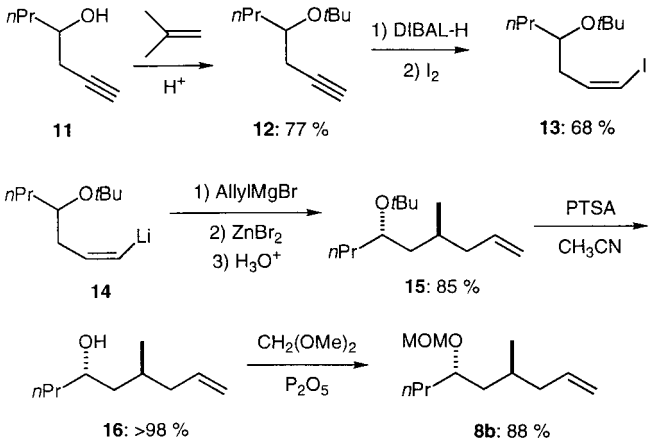
Scheme 5. Structure determinations.

of the acetal moiety and iodocyclization[9] of the resulting alcohol. The corresponding tetrahydropyrans were then subjected to ^{1}H NMR analysis and the relative configurations were determined by coupling constants and/or NOE measurements. Our results are reported in Scheme 5, and the yields of the substituted tetrahydropyrans are listed in Table 1. The iodoetherification reaction generally occurred with an excellent stereoselectivity, whereby the iodomethyl moiety

occupied the equatorial position in **10a–g**, except for compound **10f**. The compound **10fx** was obtained as a mixture of the two possible diastereomers in a 60/40 ratio and the structure determination was carried out on the major diastereomer. In the case of **8fy**, the mixture of the inseparable diastereomers, when subjected to the iodoetherification reaction, led to a mixture of three isomeric iodomethyltetrahydropyrans; among them only the major diastereomer **10fy** could be separated and subjected to ^{1}H NMR analysis.

The stereochemistry of compound **8cx** could not be determined by this methodology. However, its structure has been determined to be the one represented in Scheme 4 by analogy with the structures obtained from **1b**,[5] **6d**, and **6e** through reaction with allylzinc bromide.

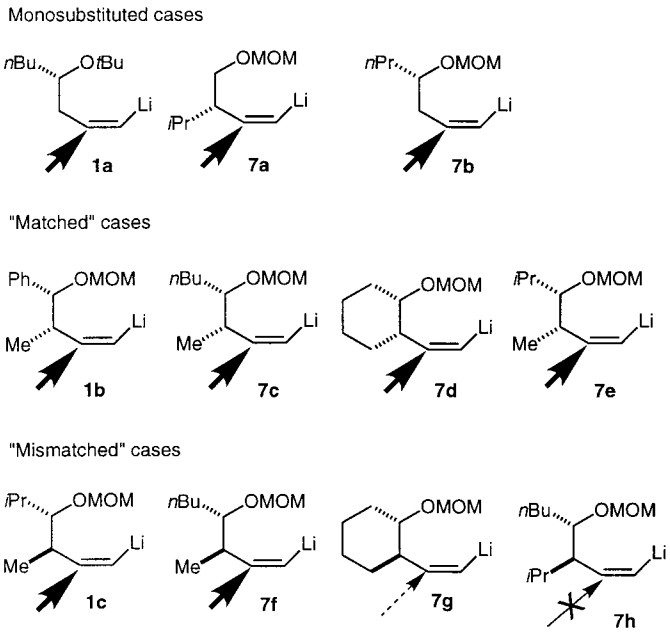
The reaction of metalated homoallylic *tert*-butyl ether **14** with allylzinc bromide gave after hydrolysis the ether **15** in 70% yield as a single diastereomer (Scheme 6). Its stereochemistry was attributed by analogy with that observed in **2a**.[5] Transformation of ether **15** into acetal **8b** was achieved in two steps. Compound **8b** prepared by this method was found to be identical to the one obtained by reaction of metalated homoallylic ether **7b** with allylzinc bromide, thus determining the stereochemical course of the latter reaction. Scheme 6 also depicts the preparation of **13** from homopropargylic alcohol **11**.



Scheme 6. Preparation of ether **15** and acetal **8b**.

Discussion

Reactions with allylzinc bromide: As seen above, the stereochemical course of the allylzincation reaction is somewhat puzzling. Clearly the stereochemistries cannot be explained only on the basis of simple steric hindrance. For monosubstituted systems, the reaction occurs on the side opposite to the substituent (reactions of **1a**, **7a**, and **7b**). For disubstituted systems, two cases have to be considered. When both substituents lie on the same side of the cycle formed through chelation ("matched" case), the reaction again occurs selectively on the side opposite to the substituents (reactions of **1b**, **7c**, **7d**, and **7e**), and this behavior can be explained by simple steric hindrance. In contrast, when the substituents are *trans* to each other in the chelate cycle ("mismatched" case), the reaction occurs on the side opposite to the homoallylic substituent (reactions of **1c** and **7f**) or to the allylic substituent (reaction with **7g**). This allylic substituent seems to have an influence on the reactivity, as in the case of an overly sterically demanding substituent (*i*Pr group in **7h**), no reaction was observed. In contrast, in the monosubstituted case of **7a**, the same sterically demanding *i*Pr group does not inhibit the reaction. These results are summarized in Scheme 7.



Scheme 7. Stereochemical course of the allylzincation reaction.

Diastereoselectivity under thermodynamic control: A first conceivable explanation for our observations could be that the reaction follows a thermodynamically controlled pathway. Calculations by Schreiner et al.[3c] have shown that in the case of the reaction of a vinyllithium compound with an allylzinc compound, the elementary allylzincation step itself is endothermic, with an energy loss of 20.2 kcal mol^{-1} between the initial Zn–Li bimetallic complex and the resultant bimetallic species, with an activation energy of 24.9 kcal mol^{-1}; similar values (energy loss: 23.2 kcal mol^{-1}, activation energy: 24.5 kcal mol^{-1}) were obtained by Nakamura et al.[3a,b] These values indicate a late transition state. In the case of the reaction of a vinylmagnesium halide with allylzinc, the calculations provided values involving a less endothermic process, as the energy loss between the initial Zn–Mg bimetallic complex and the bimetallic product was found to be only 7.1 kcal mol^{-1} by Schreiner et al. or 4.0 kcal mol^{-1} by Nakamura et al., with an energy barrier of 15.9 kcal mol^{-1} or 15.3 kcal mol^{-1}, respectively. It should be pointed out that these calculations do not involve metalated allylic or homoallylic ethers.

In such an interpretation involving an endothermic process and a late transition state, a chairlike transition state should

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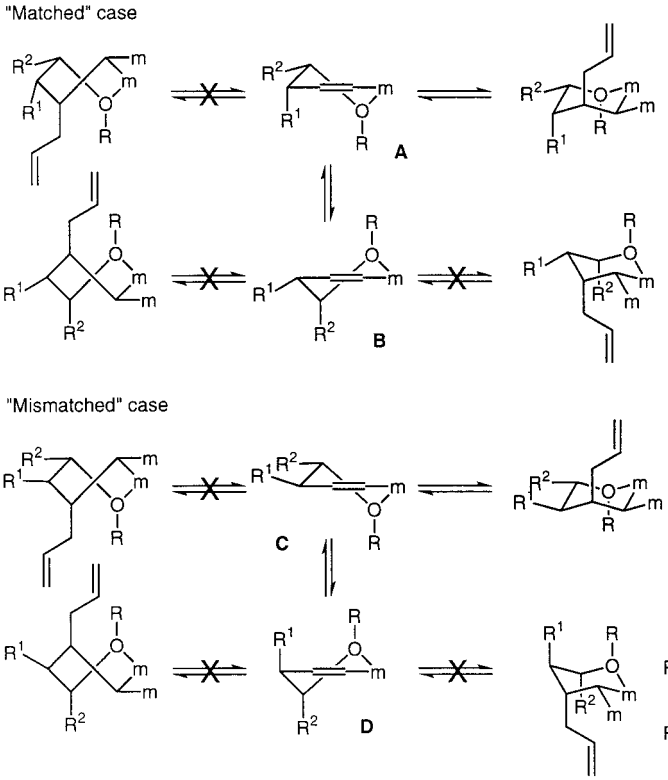
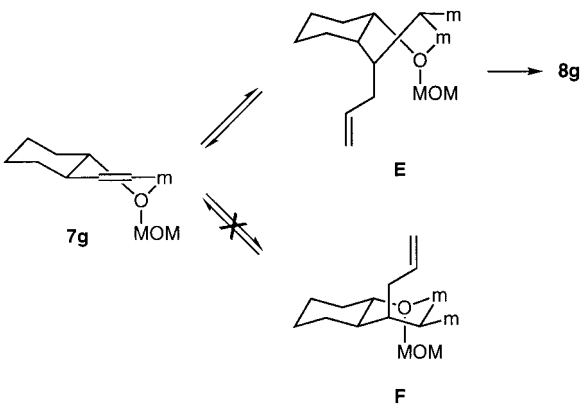
be favored over a twistlike transition state, as in the case of the halogenation of cyclohexenes,[10–12] and the stereochemistry of the allylzinc reaction should thus be governed by the homoallylic substituent alone (Scheme 8). Starting from the



Scheme 8. Late transition state control.

two possible half-chairs **A** and **B** in the "matched" case (or **C** and **D**, respectively in the "mismatched" case), two chairlike transition states are then possible; however, one (from **B** or **D**) is disfavored because of the steric interactions between the allyl moiety and the homoallylic substituent R^2.

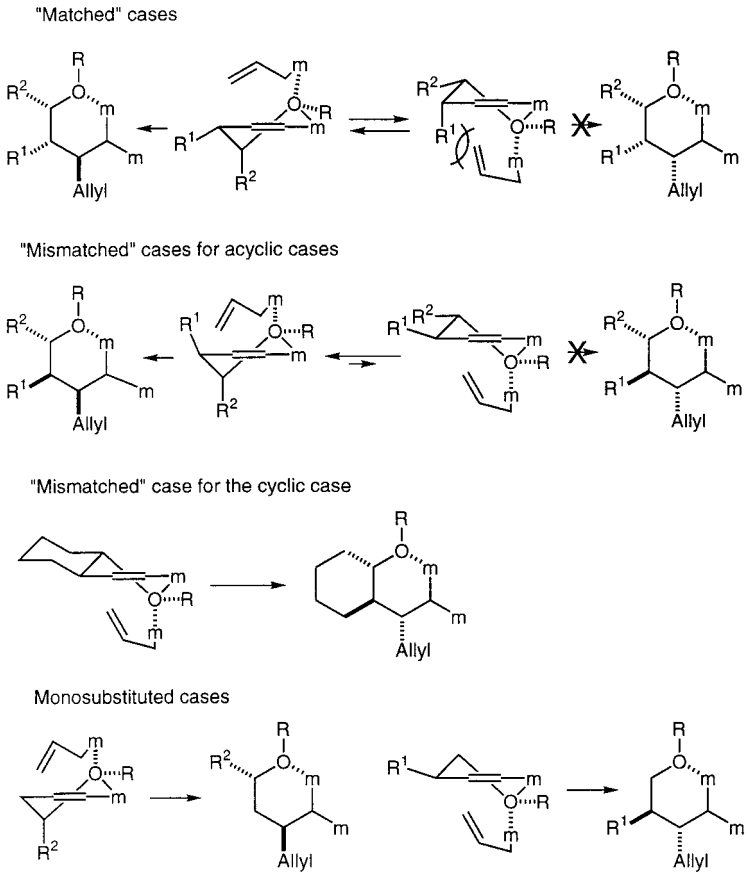
This interpretation explains almost all of the results we obtained, except for the case of the allylzincation of **7g**. In this case, such an interpretation would invoke a highly strained fused chair-twisted transition state leading to **E** (Scheme 9),



Scheme 9. Late transition state in the reaction of **7g**.

which would be highly disfavored over the other possible fused chair–chair transition state leading to **F**. It could be envisioned that in the case of **7g**, the allylzinc moiety's approach could be hindered by axial hydrogens in the cyclohexane ring. Hereby intramolecular coordination may form an eight-membered ring rather than a six-membered ring, thus altering the stereochemical course of the reaction.[13] However, another explanation is possible, in which an early transition state is followed by a kinetically controlled pathway.

Diastereoselectivity under kinetic control: Notably, the only "mismatched" case in which the allylzinc moiety reacts *syn* to the homoallylic substituent (**7g**) is also the only case in which the conformational equilibrium between the two possible half-chairs is blocked, as there is only one possible conformation depicted in Scheme 9. This then leads to consider the following assumptions: 1) in this case the allylzinc moiety reacts on the same side as the oxygen atom and *this could be the stereodifferentiating factor*, and 2) in all other "mismatched" cases, the real reacting conformer is *the one with the two substituents in an axial or pseudoaxial position* (Scheme 10). Here again, the allylzinc moiety is reacting on



Scheme 10. Chelation-controlled allylzincation reactions.

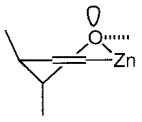
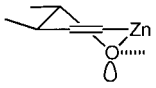
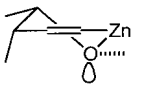
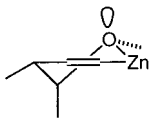
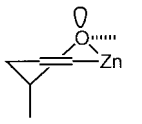
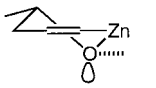
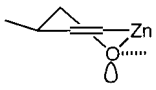
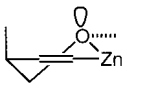
the same side as the oxygen atom. This alternate explanation involves a *kinetically controlled reaction pathway with an early transition state*. The same stereodifferentiating factor could also be invoked in the cases of monosubstituted

substrates, as well as in the "matched" cases: the reaction of the allylzinc moiety could be directed only through chelation to the oxygen atom in the most reactive conformer (Scheme 10).

Interestingly, this new approach explains all of our results. The preference in the reaction of the allylzinc moiety in the "matched" case is readily understandable (Scheme 10) on the simple basis of steric hindrance in the approach of the allyl group. In the "mismatched" case, when the R^1 and R^2 groups lie in the pseudoequatorial and equatorial positions, a strong 1,2-diequatorial strain is developed, strain similar to that observed in cyclohexenes and more significant than that observed in simple cyclohexanes.[10] In contrast, R^1 and R^2 groups in pseudoaxial and axial positions have no real steric interaction with any other group in the cycle except for the lone pair of the oxygen atom. Some cases of preference for diaxial over diequatorial situations have been reported in cyclohexenes,[12] and in 4,5-disubstituted,[14] 4,6-disubstituted,[15] 5,6-disubstituted,[16] and 4,5,6-trisubstituted[17] *6H*-4,5-dihydropyrans, as well as for other unsaturated six-membered heterocycles.[18] To confirm this hypothesis, we conducted several simple semiempirical AM1 calculations.[19] The results demonstrate a clear preference for the diaxial conformer over the diequatorial one (Table 2).

In the "mismatched" case the lower energy conformer is the one with the two substituents in the axial position, with an energy difference of 2.80 kcal mol^{-1} (Table 2). Such a significant difference could be minimized by steric interaction of the allyl moiety with the allylic pseudoaxial substituent, but the major reaction pathway should proceed through the diaxial conformer, and this is confirmed experimentally when we obtain products **2c**, **8fx**, and **8g**. It should be noted that if the allylic substituent is too sterically demanding (as an *i*Pr group in **7h**), the diequatorial conformer should be even more disfavored, but the approach of the allyl moiety on the diaxial conformer should also be disfavored. This could explain the lack of reactivity observed with **7h**. A significant difference in energy was also found in the reactions of monosubstituted substrates. Here again, the allylzinc moiety should react through the less energetic conformers in an *anti* fashion to the substituent, resulting in compounds **2a**, **8b**, and **8ax**. In contrast, in the "matched" case, the energy difference between the two possible conformers is much smaller, with a value of 0.26 kcal mol^{-1} in favor of the conformer with the two substituents on the same side of the double bond plane as the oxygen atom. However, this small difference in energy should be enhanced by the steric interaction between the allylic group in the pseudoaxial position and the reacting allyl moiety. In this case, products **1b**, **8cx**, **8d**, and **8e** are obtained. Although these calculations only concern the starting materials and not the transition states, the tendencies they reveal strongly support our hypothesis.

Table 2. AM1 calculations on the possible conformers of substituted 4-zincio-3-butenyl methyl ethers.

Lower energy conformer	Higher energy conformer	ΔE (kcal mol^{-1})
		2.80
		0.26
		2.85
		1.46

Reactions with crotylzinc reagents: It has previously been shown that crotylzinc reagents react with vinyl metal compounds in the *cisoid* form stereoselectively.[2] In the monosubstituted and "matched" cases **6a** and **6c**, the stereoselectivity was also very good in favor of the reaction of *cisoid* crotylzinc compounds to produce **8ay** and **8cy** (Table 1, entries 2 and 5). In the "mismatched" case of **6f**, the stereoselectivity was poorer, as two diastereomers were obtained in a 68/32 ratio. It has previously been shown[5] that in the "mismatched" case **1c**, the reaction of the crotylzinc reagent also occurred with a lower diastereoselectivity than in the "matched" case, and two diastereomers were obtained in a 75/25 ratio. This lack of selectivity was shown not to be caused by lower facial selectivity, but rather by a reaction, to a minor extent, of the *transoid* form of crotylzinc reagent. Unfortunately we were unable to determine the stereochemistry of the minor diastereomer we obtained in the reaction of **6f**, and we are thus unable to confirm the generality of this observation. However, this drop of selectivity in the "mismatched" case is understandable, as the reaction occurs on the diaxial conformer, and the steric interactions between the allylic substituent and the crotylzinc reagent must thus be enhanced with respect to the interactions with allylzinc reagents. We are currently working to understand more about these reactions, and further results will be reported in due course.

Conclusions

The reaction of allylzinc and crotylzinc reagents with metalated mono- or disubstituted homoallylic ethers occurs smoothly with excellent diastereoselectivity. The diastereoselectivity of the reaction is governed mostly by an attack *anti* to the homoallylic substituent. This stereoselectivity can be attributed to a kinetically controlled addition directed by chelation onto the oxygen atom. The addition occurs to the energetically favored conformer, this being the diaxial one for *syn*-disubstituted homoallylic ethers. It should be emphasized that this methodology allows the totally diastereoselective construction of 1,2,3-trisubstituted or 1,2,3,4-tetrasubstituted 5-hexenylethers. Applications to the diastereoselective and enantioselective synthesis of natural products is currently under investigation.

0947-6539/02/0814-3144 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 14

Experimental Section

The preparation and physical data for ethers **4a**, **4b**, **4d**, **4e**, **4g**; for alkynyl iodides **5a–h**; for vinyl iodides **6a–h**; as well as for compounds **12**, **13**, **15**, and **16;** are reported as Supporting Information.

General procedure for the preparation of ethers 8a–h: Under a nitrogen atmosphere, *tert*-butyllithium (1.7 M in pentane, 2.0 equiv) was added to a stirred solution of vinyl iodide **6a–h** (0.1 M) in anhydrous Et_2O at $-80\,^{\circ}C$. The resulting mixture was warmed up to $-55\,^{\circ}C$ for 30 min and allylmagnesium or crotylmagnesium bromide (etheral solutions, 4.0 equiv) and $ZnBr_2$ (1.0 M in Et_2O, 4.0 equiv) were added successively. After warming to $-25\,^{\circ}C$ and stirring for 3–7 h, the solution was quenched with 1 M HCl and the aqueous layer was extracted with Et_2O (three times). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, water, and brine, dried over anhydrous $MgSO_4$, and then concentrated in vacuo. The residual oils were purified by flash chromatography, by eluting with 5% ethyl acetate/cyclohexane to give ethers **8a–h**.

(4*R,5*R**)-5-isopropyl-6-methoxymethoxy-4-methylhex-1-ene (8ax)**: Prepared from (*Z*)-vinyl iodide **6a** (568 mg, 2.00 mmol) and allylmagnesium bromide in 74% yield (296 mg, 1.48 mmol) as a yellow oil, d.r.: >98/2. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.77$ (ddd, $^3J = 7.1$, 10.1, and 17.1 Hz, 1H), 5.05–4.99 (m, 2H), 4.63 (s, 2H), 3.57 (ABX system, $^3J = 5.0$ Hz, $^2J = 10.1$ Hz, 1H), 3.51 (ABX system, $^3J = 5.1$ Hz, $^2J = 10.1$ Hz, 1H), 3.39 (s, 3H), 2.17 (m, 1H), 2.02 (m, 1H), 1.86–1.80 (m, 2H), 1.34 (m, 1H), 0.95 (d, $^3J = 6.9$ Hz, 6H), 0.87 (d, $^3J = 6.7$ Hz, 3H); ^{13}C NMR (100.6 MHZ, $CDCl_3$): $\delta = 138.1$, 115.7, 96.7, 66.9, 55.4, 47.7, 40.6, 32.6, 28.0, 21.3, 20.4, 16.0; elemental analysis calcd (%) for $C_{12}H_{24}O_2$ (200.18): C 71.95, H 12.08; found: C 71.74, 12.16.

(3*S,4*S**,5*S**)-3,4-Dimethyl-5-*iso*-propyl-6-methoxymethoxyhex-1-ene (8ay)**: Prepared from (*Z*)-vinyl iodide **6a** (196 mg, 0.69 mmol) and crotylmagnesium bromide in 59% yield (86 mg, 0.40 mmol) as a yellow oil, d.r.: >98/2. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.71$ (ddd, $^3J = 8.2$, 10.2, and 17.3 Hz, 1H), 4.98 (m, 2H), 3.52 (ABX system, $^3J = 4.1$ and 5.6 Hz, $^2J = 9.7$ Hz, 2H), 3.39 (s, 3H), 2.23 (m, 1H), 1.89 (m, 1H), 1.55 (m, 1H), 1.44 (m, 1H), 1.03 (d, $^3J = 6.6$ Hz, 3H), 0.95 (d, $^3J = 7.1$ Hz, 3H), 0.93 (d, $^3J = 6.6$ Hz, 3H), 0.82 (d, $^3J = 7.1$ Hz, 3H); ^{13}C NMR (100.6 MHZ, $CDCl_3$): $\delta = 143.5$, 113.9, 97.1, 67.6, 55.7, 45.7, 42.2, 37.3, 28.5, 21.0, 20.6, 19.2, 13.3; IR (film, KBr): $\tilde{\nu} = 3030$, 2960, 2940, 2880, 1635 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{26}O_2$ (214.34): C 72.84, H 12.23; found: C 72.76, 12.36.

(4*S,6*S**)-6-methoxymethoxy-4-methylnon-1-ene (8b)**: Prepared from (*Z*)-vinyl iodide **6b** (284 mg, 1.00 mmol) and allylmagnesium bromide in 70% yield (140 mg, 0.70 mmol) as a yellow oil, d.r.: >98/2. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (ddd, $^3J = 7.1$, 10.4, and 17.4 Hz, 1H), 5.05 (dd, $^2J = 0.8$ Hz, $^3J = 9.5$ Hz, 1H), 5.02 (dd, $^2J = 0.8$ and $^3J = 17.6$ Hz, 1H), 4.67 (AB system, $^2J = 6.9$ Hz, 2H), 3.67 (m, 1H), 3.40 (s, 3H), 2.50–1.93 (m, 2H), 1.86–1.70 (m, 1H), 1.58–1.20 (m, 6H), 0.95–0.91 (m, 6H); ^{13}C NMR (100.6 MHZ, $CDCl_3$): $\delta = 137.7$, 116.2, 95.7, 75.5, 55.9, 42.4, 42.0, 39.5, 29.4, 19.7, 18.8, 14.7; IR (film, KBr): $\tilde{\nu} = 3080$, 2960, 2930, 2880, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{24}O_2$ (212.23): C 71.95, H 12.08; found: C 71.73, 12.19.

(4*S,5*S**,6*S**)-4,5-Dimethyl-6-methoxymethoxydec-1-ene (8cx)**: Prepared from (*Z*)-vinyl iodide **6c** (621 mg, 2.00 mmol) and allylmagnesium bromide in 52% yield (238 mg, 1.04 mmol) as a yellow oil, d.r.: >98/2. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (m, 1H), 5.01 (m, 2H), 4.65 (AB system, $^2J = 6.8$ Hz, 2H), 3.58 (m, 1H), 3.39 (s, 3H), 2.19 (m, 1H), 1.85 (m, 1H), 1.70–1.25 (m, 8H), 0.90 (m, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 138.1$, 116.0, 96.4, 80.2, 56.0, 40.5, 37.6, 34.6, 32.1, 27.9, 23.4, 18.4, 14.5, 11.3; IR (film, KBr): $\tilde{\nu} = 3060$, 2940, 2880, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{28}O_2$ (228.37): C 73.63, H 12.36; found: C 73.37, 12.48.

(3*S,4*S**,5*S**,6*S**)-6-Methoxymethoxy-3,4,5-trimethyldec-1-ene (8cy)**: Prepared from (*Z*)-vinyl iodide **6c** (624 mg, 2.00 mmol) and crotylmagnesium bromide in 71% yield (344 mg, 1.42 mmol) as a yellow oil, d.r.: >98/2. ^1H NMR (400 MHz, CDCl): $\delta = 5.74$ (m, 1H), 5.00 (m, 2H), 4.64 (AB system, $^2J = 7.1$ Hz, 2H), 3.67 (ddd, $^3J = 2.0$, 6.1, and 7.6 Hz, 1H), 3.37 (s, 3H), 2.49 (m, 1H), 1.70–1.15 (m, 8H), 1.04 (d, $^3J = 7.0$ Hz, 3H), 0.94 (d, $^3J = 6.6$ Hz, 3H), 0.92 (t, $^3J = 7.1$ Hz, 3H), 0.87 (d, $^3J = 6.7$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 140.9$, 114.6, 96.3, 79.3, 55.9, 40.3, 39.4, 38.6, 32.5, 28.7, 23.3, 19.8, 14.5, 12.5, 11.9; IR (film, KBr): $\tilde{\nu} = 3030$, 2960, 2880, 1630 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{30}O_2$ (242.40): C 74.32, H 12.47; found: C 74.09, 12.53.

(1*S,2*S**)-1-Methoxymethoxy-2-(1-[(1*S**)-1-methylbut-3-enyl])cyclohexane (8d)**: Prepared from (*Z*)-vinyl iodide **6d** (590 mg, 1.99 mmol) and allylmagnesium bromide in 51% yield (214 mg, 1.01 mmol) as a yellow oil, d.r.: >98/2. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (m, 1H), 5.01 (m, 2H), 4.68 (AB system, $^2J = 6.8$ Hz, 2H), 3.93 (m, 1H), 3.41 (s, 3H), 2.29 (m, 1H), 2.03 (m, 1H), 1.95–1.05 (m, 10H), 0.93 (d, $^3J = 6.7$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 138.0$, 116.1, 95.6, 73.8, 56.1, 46.6, 38.7, 34.1, 30.7, 26.7, 24.9, 20.7, 17.4; IR (film, KBr): $\tilde{\nu} = 3030$, 2950, 2880, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{24}O_2$ (212.23): C 73.54, H 11.39; found: C 73.36, 11.52.

(4*S,5*S**,6*S**)-6-Methoxymethoxy-4,5,7-trimethyloct-1-ene (8e)**: Prepared from (*Z*)-vinyl iodide **6e** (590 mg, 1.98 mmol) and allylmagnesium bromide in 72% yield (304 mg, 1.42 mmol) as a yellow oil, d.r.: >98/2. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (m, 1H), 5.01 (m, 2H), 4.68 (s, 2H), 3.41 (s, 3H), 3.25 (t, $^3J = 5.0$ Hz, 1H), 2.17 (m, 2H), 1.90–1.50 (m, 3H), 0.91 (m, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.6$, 115.5, 98.3, 86.2, 55.8, 39.9, 37.0, 34.6, 30.8, 19.8, 17.9, 11.2; IR (film, KBr): $\tilde{\nu} = 3030$, 2950, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{26}O_2$ (214.34): C 72.84, H 12.23; found: C 72.52, 12.30.

(4*S,5*R**,6*S**)-4,5-Dimethyl-6-methoxymethoxydec-1-ene (8fx)**: Prepared from (*Z*)-vinyl iodide **6f** (626 mg, 2.02 mmol) and allylmagnesium bromide in 79% yield (365 mg, 1.59 mmol) as a colorless oil, d.r.: >98/2. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (m, 1H), 5.02 (m, 2H), 4.64 (s, 2H), 3.53 (m, 1H), 3.40 (s, 3H), 2.15–1.90 (m, 2H), 1.85–1.25 (m, 8H), 0.92 (t, $^3J = 6.7$ Hz, 3H), 0.85 (d, $^3J = 6.8$ Hz, 3H), 0.79 (d, $^3J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.7$, 115.84, 96.0, 79.9, 55.7, 40.2, 39.3, 32.9, 30.4, 27.2, 23.2, 15.2, 14.3, 10.5; IR (film, KBr): $\tilde{\nu} = 3030$, 2960, 2920, 2880, 1630 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{28}O_2$ (228.37): C 73.63, H 12.36; found: C 73.25, 12.43.

(3*S,4*S**,5*R**,6*S**)-6-Methoxymethoxy-3,4,5-trimethyldec-1-ene (8fy)**: Prepared from (*Z*)-vinyl iodide **6f** (624 mg, 2.01 mmol) and crotylmagnesium bromide in 65% yield (317 mg, 1.31 mmol) as a yellow oil; mixture of two diastereomers, d.r.: 68/32. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.73$ (m, 1H), 4.99 (m, 2H), 4.64 (AB system, $^2J = 6.2$ Hz, 2H), 3.58 (m, 1H *maj*), 3.50 (m, 1H *min*), 3.40 (s, 3H *min*), 3.39 (s, 3H *maj*), 2.16 (m, 1H), 1.80–1.30 (m, 8H), 1.01 (d, $^3J = 6.8$ Hz, 3H *maj*), 0.98 (d, $^3J = 7.0$ Hz, 3H *min*), 0.95–0.80 (m, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 144.4$ (*min*), 142.6 (*maj*), 113.8 (*maj*), 112.9 (*min*), 95.9 (*min*), 95.7 (*maj*), 79.8 (*min*), 79.3 (*maj*), 55.7, 40.5, 38.0, 37.1, 30.1, 27.1, 23.4, 19.2, 14.5, 12.5, 11.2; IR (film, KBr): $\tilde{\nu} = 3030$, 2950, 2880, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{30}O_2$ (242.40): C 74.32, H 12.47; found: C 74.07, 12.59.

(1*S,2*R**)-1-Methoxymethoxy-2-(1-[(1*R**)-1-methylbut-3-enyl])cyclohexane (8g)**: Prepared from (*Z*)-vinyl iodide **6g** (886 mg, 2.99 mmol) and allylmagnesium bromide in 65% yield (414 mg, 1.95 mmol) as a pale orange oil; mixture of two diastereomers, d.r.: 90/10. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.76$ (m, 1H), 4.98 (m, 2H), 4.67 (AB system, $^2J = 6.9$ Hz, 2H), 3.47 (m, 1H), 3.37 (s, 3H), 2.22 (m, 1H), 2.10 (m, 1H), 1.71–0.98 (m, 10H), 0.88 (d, $^3J = 6.9$ Hz, 3H *maj*), 0.77 (d, $^3J = 6.9$ Hz, 3H *min*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 139.1$, 115.5, 95.5, 77.3, 56.1, 49.3, 36.1, 33.1, 26.1, 25.2, 31.3, 18.0; IR (film, KBr): $\tilde{\nu} = 3040$, 2960, 2940, 2880, 1630 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{24}O_2$ (212.23): C 73.54, H 11.39; found: C 73.33, 11.59.

General procedure for the preparation of tetrahydropyrans 10a–g: A few drops of HCl (2 M) were added dropwise to a stirred solution of methoxymethyl ethers **8a–g** (0.1 M) in absolute methanol. The resulting solution was then refluxed for 4 h, cooled to 25 °C, quenched by a saturated aqueous $NaHCO_3$ solution, and then extracted with Et_2O (three times). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and the solvents were removed in vacuo to give intermediate alcohols, which were used in the next step without purification.

Under a nitrogen atmosphere, iodine (1.50 equiv) was added to a stirred 0.1 M solution of the above crude alcohols in dry CH_3CN at $-35\,^{\circ}C$. The resulting mixture was then slowly warmed to 25 °C. After stirring overnight at this temperature, the solution was quenched with a saturated aqueous $Na_2S_2O_3$ solution, and the aqueous layer was extracted with Et_2O (four times). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and then concentrated in vacuo. The residual oils were purified by flash chromatography, by eluting with 10% ethyl acetate/cyclohexane to give tetrahydropyrans **10a–g**.

(2*S,4*R**,5*R**)-2-Iodomethyl-5-isopropyl-4-methyltetrahydropyran (10ax)**: The intermediate alcohol was prepared from methoxymethyl ether **8ax** (200 mg, 1.00 mmol, d.r.: >98/2) in 78% yield (121 mg, 0.78 mmol) as a colorless oil, d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (ddd, $^3J =$ 7.1, 10.1, and 17.2 Hz, 1H), 5.06–5.00 (m, 2H), 3.72 (ABX system, $^3J = 5.0$, 5.0 Hz, $^2J = 11.2$ Hz, 2H), 2.17 (m, 1H), 2.05 (m, 1H), 1.84 (m, 2H), 0.98 (d, $^3J = 6.6$ Hz, 3H), 0.96 (d, $^3J = 6.2$ Hz, 3H), 0.89 (d, $^3J = 7.7$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 138.1$, 115.9, 61.7, 50.3, 40.7, 32.4, 27.7, 21.4, 20.5, 16.2.

The title product **10ax** was prepared from the above crude intermediate alcohol (104 mg, 0.66 mmol) in 73% yield (135 mg, 0.48 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.94$ (dd, ^3J*(ax-eq)* $= 2.8$ Hz, $^2J = 11.4$ Hz, 1H) 3.49 (m, 1H), 3.41 (t, $^2J = {}^3J$*(ax-ax)* $=$ 11.4 Hz, 1H), 3.16 (ABX system, $^3J = 4.6$ and 6.6 Hz, $^2J = 10.2$ Hz, 2H), 2.19 (m, 1H), 1.67 (dt, $^2J = 10.7$ Hz, ^3J*(ax-eq)* $= 2.4$ Hz, 1H), 1.54 (dt, ^3J*(ax-eq)* $= 4.7$ Hz, $^2J = {}^3J$*(ax-ax)* $= 11.6$ Hz, 1H), 1.34 (m, 2H), 0.96 (d, $^3J =$ 7.2 Hz, 3H), 0.92 (d, $^3J = 6.9$ Hz, 3H), 0.89 (d, $^3J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 71.1$, 66.6, 45.5, 39.5, 27.4, 26.3, 21.1, 20.4, 12.2, 10.9; IR (film, KBr): $\tilde{\nu} = 2960$, 2920, 2860, 1445 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{19}IO$ (282.16): C 42.57, H 6.79; found: C 42.49, 6.85.

(2*S,3*S**,4*S*,5*R**)-3,4-Dimethyl-2-iodomethyl-5-isopropyltetrahydropyran (10ay)**: The intermediate alcohol was prepared from methoxymethyl ether **8ay** (44 mg, 0.20 mmol, d.r.: >98/2) in 65% yield (22 mg, 0.13 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.78$ (m, 1H), 5.02 (m, 2H), 3.71 (m, 1H), 2.25–1.05 (m, 11H), 0.95 (d, $^3J = 6.9$ Hz, 3H), 0.93 (d, $^3J = 7.0$ Hz, 3H), 0.91 (d, $^3J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.1$, 116.0, 73.1, 42.6, 38.3, 35.9, 28.7, 23.2, 18.0, 14.5, 10.5.

The title product **10ay** was then prepared from the above crude intermediate alcohol (213 mg, 1.25 mmol) in 72% yield (266 mg, 0.90 mmol) as a pale yellow oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.92$ (ddd, $^4J = 1.0$ Hz, ^3J*(ax-eq)* $= 4.0$ Hz, ^2J*(ax-ax)* $= 11.2$ Hz, 1H), 3.26 (t, ^3J*(ax-ax)* $= {}^2J = 11.2$ Hz, 1H), 3.13 (ABX system, $^3J = 2.5$ and 5.1 Hz, $^2J = 10.7$ Hz, 2H), 2.52 (ddd, $^3J = 2.5$ and 5.1 Hz, ^3J*(ax-ax)* $= 9.6$ Hz, 1H), 1.74 (m, 1H), 1.64 (m, 1H), 1.36 (m, 1H), 1.16 (m, 1H), 0.79 (d, $^3J = 6.6$ Hz, 3H), 0.75 (d, $^3J = 6.6$ Hz, 3H), 0.60 (d, $^3J = 7.1$ Hz, 3H), 0.56 (d, $^3J = 6.6$ Hz, 3H); ^{13}C NMR (100.6 MHz, C_6D_6/TMS): $\delta = 74.2$, 66.0, 48.1, 40.6, 33.9, 26.5, 21.3, 20.5, 15.2, 12.7, 6.7; IR (film, KBr): $\tilde{\nu} = 2940$, 2860, 1445 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{21}IO$ (296.19): C 44.61, H 7.15; found: C 44.77, 7.23.

(2*S,3*R**,4*R**,5*S**,6*S**)-6-Butyl-2-iodomethyl-3,4,5-trimethyltetrahydropyran (10cy)**: The intermediate alcohol was prepared from methoxymethyl ether **8cy** (344 mg, 1.04 mmol, d.r.: >98/2) in 94% yield (188 mg, 0.84 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.75$ (m, 1H), 4.98 (m, 2H), 3.77 (m, 1H), 2.50 (m, 1H), 1.70–1.20 (m, 8H), 1.04 (d, $^3J = 6.9$ Hz, 3H), 0.93 (m, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 141.0$, 114.3, 72.0, 40.7, 40.3, 38.9, 35.9, 27.0, 22.9, 19.5, 14.2, 12.1, 10.6.

The title product **10cy** was then prepared from the above crude intermediate alcohol (188 mg, 0.95 mmol) in 78% yield (239 mg, 0.74 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.61$ (ddd, ^3J*(ax-eq)* $= 2.7$ Hz, $^3J = 6.6$ and 7.8 Hz, 1H) 3.36 (ddd, $^3J =$ 2.7 and 4.6 Hz, ^3J*(ax-ax)* $= 7.8$ Hz, 1H), 3.21 (ABX system, $^3J = 6.6$ and 7.8 Hz, $^2J = 9.9$ Hz, 2H), 1.90 (m, 1H), 1.82 (m, 1H), 1.70–1.20 (m, 7H), 1.04 (d, $^3J = 7.2$ Hz, 3H), 0.93 (t, $^3J = 7.0$ Hz, 3H), 0.81 (d, $^3J = 7.2$ Hz, 3H), 0.80 (d, $^3J = 7.2$ Hz, 3H) ; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 83.7$, 83.0, 38.8, 37.0, 36.7, 32.3, 28.7, 23.2, 17.4, 14.5, 9.5, 8.4, 7.5; IR (film, KBr): $\tilde{\nu} =$ 2950, 2920, 2860, 1445 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{25}IO$ (324.24): C 48.16, H 7.77; found: C 48.01, 7.88.

(2*S,4*S**,4a*S**,8a*S**)-2-Iodomethyl-4-methyloctahydrochromene (10d)**: The intermediate alcohol was prepared from methoxymethyl ether **8d** (214 mg, 1.00 mmol) in 60% yield (101 mg, 0.60 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.80$ (m, 1H), 5.04 (m, 2H), 4.11 (br s, 1H), 3.92 (m, 1H), 2.29 (m, 2H), 2.00–1.10 (m, 10H), 0.96 (d, $^3J = 6.8$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.7$, 116.2, 69.4, 40.1, 34.3, 33.4, 26.7, 25.6, 24.5, 20.9, 17.2.

The title product **10d** was then prepared from the above crude intermediate alcohol (101 mg, 0.60 mmol, d.r.: >98/2) in 50% yield (86 mg, 0.30 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.50 (m, 1H), 3.27 (m, 3H), 1.90 (m, 1H), 1.60–1.05 (m, 10H), 0.91 (d, $^3J =$ 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 76.5$, 72.0, 40.5, 35.0, 33.4, 32.5, 26.2, 21.3, 20.1, 19.0, 11.9; IR (film, KBr): $\tilde{\nu} = 2950$, 2910, 2860, 1445 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{19}IO$ (294.17): C 44.91, H 6.51; found: C 44.81, 6.59.

(2*S,4*S**,5*S**,6*S**)-4,5-Dimethyl-2-iodomethyl-6-isopropyltetrahydropyran (10e)**: The intermediate alcohol was prepared from methoxymethyl ether **8e** (304 mg, 1.42 mmol) in 88% yield (213 mg, 1.25 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.80$ (m, 1H), 5.00 (m, 2H), 3.32 (dd, $^3J = 3.9$ and 7.2 Hz, 1H), 2.25–1.50 (m, 5H), 0.97 (d, $^3J = 6.6$ Hz, 3H), 0.95 (d, $^3J = 6.7$ Hz, 3H), 0.92 (d, $^3J = 7.0$ Hz, 3H), 090 (d, $^3J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 138.2$, 116.0, 73.4, 39.8, 38.2, 35.5, 31.6, 19.9, 18.7, 17.9, 10.5.

The title product **10e** was then prepared from the crude intermediate alcohol (213 mg, 1.25 mmol, d.r.: >98/2) in 72% yield (266 mg, 0.90 mmol) as a colorless oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.37$ (m, 1H), 3.19 (dd, $^3J = 4.8$ Hz, $^2J = 7.3$ Hz, 2H), 2.85 (dd, ^3J*(ax-eq)* $= 2.0$ Hz, $^3J = 9.8$ Hz, 1H), 1.85–1.60 (m, 4H), 1.52 (dt, ^3J*(ax-eq)* $= 3.0$, $^2J = 13.0$ Hz, 1H), 1.06 (d, $^3J = 6.4$ Hz, 3H), 0.95 (d, $^3J = 7.0$ Hz, 3H), 0.83 (d, $^3J = 6.8$ Hz, 3H), 0.74 (d, $^3J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 88.5$, 78.1, 34.9, 34.8, 34.2, 30.0, 20.8, 19.7, 18.5, 10.1, 5.6; IR (film, KBr): $\tilde{\nu} = 2950$, 2880, 1440 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{21}IO$ (296.19): C 44.61, H 7.15; found: C 44.57, 7.21.

(2*S,4*S**,5*R**,6*S**)-6-Butyl-4,5-dimethyl-2-iodomethyltetrahydropyran (10fx)**: The intermediate alcohol was prepared from methoxymethyl ether **8fx** (164 mg, 0.72 mmol) in 93% yield (124 mg, 0.67 mmol) as a colorless oil, d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.78$ (m, 1H), 5.01 (m, 2H), 3.46 (m, 1H), 1.99 (m, 3H), 1.60–1.25 (m, 7H) 0.93 (t, $^3J = 6.9$ Hz, 3H), 0.82 (d, $^3J = 6.3$ Hz, 3H), 0.75 (d, $^3J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 138.4$, 115.9, 74.1, 42.3, 40.5, 34.7, 32.5, 28.2, 23.2, 14.5, 14.2, 10.4.

The title products **10fx** were then prepared from the above crude intermediate alcohol (124 mg, 0.67 mmol, d.r.: >98/2) in 82% yield (169 mg, 0.55 mmol) as a colorless oil; mixture of two diastereomers which could be separated by chromatography, d.r.: 60/40. For the major product: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.40$ (ddt, ^3J*(ax-eq)* $= 1.8$ Hz, $^3J = 6.2$ Hz, ^3J*(ax-ax)* $= 10.0$ Hz, 1H), 3.17 (d, $^3J = 6.3$ Hz, 2H), 2.96 (dt, $^3J = 9.8$ Hz, ^3J*(ax-ax)* $= 8.8$ Hz, 1H), 1.83 (ddd, ^3J*(ax-eq)* $= 1.9$ and 3.9 Hz, $^2J = 12.8$ Hz, 1H), 1.70–1.25 (m, 8H), 0.99 (m, 1H), 0.96 (d, $^3J = 6.5$ Hz, 3H), 0.92 (t, $^3J = 7.2$ Hz, 3H), 0.85 (d, $^3J = 6.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 83.7$, 76.9, 42.2, 40.6, 36.8, 33.2, 28.0, 23.0, 20.2, 14.5, 14.3, 10.2; IR (film, KBr): $\tilde{\nu} = 2950$, 2880, 1440 cm^{-1}; for the minor product: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 4.12$ (m, 1H), 3.42 (ABX system, $^3J = 6.8$ and 8.6 Hz, $^2J = 10.2$ Hz, 1H), 3.12 (m, 1H), 1.83 (ddd, ^3J*(ax-eq)* $= 1.4$ and 4.0 Hz, $^2J = 13.7$ Hz, 1H), 1.64 (m, 1H), 1.53 (m, 1H), 1.45–1.20 (m, 8H), 0.94 (d, $^3J = 6.4$ Hz, 3H), 0.91 (t, $^3J = 7.0$ Hz, 3H), 0.86 (d, $^3J = 6.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 74.7$, 73.3, 42.5, 36.3, 33.5, 31.2, 28.1, 23.3, 20.4, 14.8, 14.5, 7.7; IR (film, KBr): $\tilde{\nu} = 2950$, 2920, 2880, 1440 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{23}IO$ (310.21): C 46.46, H 7.47; found: C 46.34, 7.56.

(2*S,3*R**,4*R**,5*R**,6*S**)-6-Butyl-2-iodomethyl-3,4,5-trimethyltetrahydropyran (10fy)**: The intermediate alcohol was prepared from methoxymethyl ether **8fy** (317 mg, 1.31 mmol, d.r.: > 68/32) in 95% yield (246 mg, 1.24 mmol) as a colorless oil, d.r.: > 68/32. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.70$ (m, 1H), 4.96 (m, 2H), 3.47 (m, 1H), 2.05 (m, 1H), 1.70–1.25 (m, 8H), 1.01 (d, $^3J = 6.1$ Hz, 3H *min*), 0.99 (d, $^3J = 6.5$ Hz, 3H *maj*), 0.93 (m, 3H), 0.82 (d, $^3J = 6.9$ Hz, 3H *min*), 0.79 (d, $^3J = 6.8$ Hz, 3H *maj*), 0.75 (d, $^3J = 6.8$ Hz, 3H *maj*), 0.72 (d, $^3J = 6.8$ Hz, 3H *min*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.9$(*min*), 144.4 (*maj*), 113.7 (*maj*), 113.6 (*min*), 74.3 (*maj*), 74.2 (*min*), 42.2, 39.9, 37.3, 34.6, 28.3, 23.2, 19.1, 14.5, 12.3, 10.7.

From the above crude intermediate alcohol (246 mg, 1.24 mmol), a mixture of three diastereomers was obtained. The major one **10fy** could then be purified by chromatography in 60% yield (242 mg, 0.75 mmol) as a pale orange oil; d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.60$ (dt, ^3J*(ax-eq)* $= 2.0$ Hz, $^3J = 6.2$ Hz, 1H), 3.18 (ABX system, $^3J = 6.2$ and 8.0 Hz, $^2J =$ 10.0 Hz, 2H), 2.92 (dt, ^3J*(ax-eq)* $= 2.4$ Hz, ^3J *(ax-ax)* $= 9.0$ Hz, 1H), 1.82 (ddq, ^3J*(ax-eq)* $= 2.0$ and 4.0 Hz, $^3J = 6.6$ Hz, 1H), 1.75 (m, 8H), 0.95 (d, $^3J = 6.6$ Hz, 3H), 0.92 (t, $^3J = 7.1$ Hz, 3H), 0.80 (d, $^3J = 6.6$ Hz, 3H), 0.75 (d, $^3J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 84.4$, 81.6, 41.3, 37.8, 36.4, 33.3, 28.2, 23.1, 17.9, 14.7, 14.6, 7.8, 5.8; IR (film, KBr): $\tilde{\nu} = 2940$, 2920, 2880, 1445 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{25}IO$ (324.24): C 48.16, H 7.77; found: C 48.05, 7.83.

  0947-6539/02/0814-3146 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 14

(2*S,4*S**,4a*R**,8a*S**)-2-Iodomethyl-4-methyloctahydrochromene (10g)**: The intermediate alcohol was prepared from methoxymethyl ether **8g** (242 mg, 1.14 mmol) in 96% yield (184 mg, 1.10 mmol) as a colorless oil, d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.82$ (m, 1H), 5.02 (m, 2H), 3.48 (m, 1H), 2.19 (m, 1H), 1.98 (m, 2H), 1.91 (br s, 1H), 1.65 (m, 4H), 1.25 (m, 4H), 0.95 (m, 1H), 0.93 (d, $^3J = 7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 139.2$, 115.5, 71.8, 50.8, 36.7, 36.6, 32.2, 26.2, 25.5, 25.3, 17.9.

The title product **10g** was then prepared from the above crude intermediate alcohol (86 mg, 0.51 mmol, d.r.: >98/2) in 59% yield (91 mg, 0.30 mmol) as a colorless oil, d.r.: >98/2. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.61$ (m, 1H), 3.34 (m, 1H), 3.15 (ABX system, $^3J = 1.9$ Hz, $^2J = 12.6$ Hz, 2H), 1.95 (m, 2H), 1.70 (m, 4H), 1.60–1.15 (m, 6H), 0.89 (d, $^3J = 7.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 75.3$, 71.7, 44.7, 39.8, 33.2, 30.6, 29.0, 26.4, 25.3, 13.8, 10.9; IR (film, KBr): $\tilde{\nu} = 2940$, 2880, 1440 cm^{-1}; elemental analysis calcd (%)for $C_{11}H_{19}IO$ (294.17): C 44.91, H 6.51; found: C 44.87, 6.65.

Acknowledgement

We thank Monique Baudry and Mathilde Mahet for the preparation of starting materials, and the Ministère de l'Enseignement Supérieur et de la Recherche for a grant (to N. B.).

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Received: November 30, 2001
Revised: February 27, 2002 [F3713]

  0947-6539/02/0814-3147 $ 17.50+.50/0