From Amino Acids To Dihydrofurans: Functionalized Allenes in Modern Organic Synthesis

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Abstract: In this account, recent accomplishments in the field of target-oriented synthesis involving allenes are summarized. Allenic α-amino acid derivatives **9**, which are of interest as possible vitamin B_6 decarboxylase inhibitors, were prepared by 1,6-addition of the cyano-Gilman reagent *t*-$Bu_2CuLi{\cdot}LiCN$ to 2-amino-substituted enynoates **8**, and selective deprotection at either the amino or the ester group was realized. 2,5-Dihydrofurans **18** were obtained by cyclization of the corresponding α-hydroxyallenes; for this step, new methods (treatment with hydrogen chloride gas or acidic ion exchange resin; gold(III)-chloride catalysis) were developed. The 2-hydroxy-3,4-dienoates **14** were obtained by diastereoselective oxidation of titanium enolates formed from 3,4-dienoates **12** with dimethyl dioxirane (DMDO), whereas hydroxyallenes **16** were prepared by copper-mediated S_N2'-substitution of propargylic epoxides **15**.

Key words: allenes, amino acids, gold catalysis, 2,5-dihydrofurans, organocopper reagents

1 Introduction

In recent years, functionalized allenes have gained more and more interest not only as valuable synthetic precursors in the generation of complex molecules of biological and industrial importance but also as target molecules in natural product synthesis. Application of allenic intermediates in modern organic synthesis are mainly due to their high reactivity and inherent axial chirality, thus allowing subsequent transformations to proceed stereoselectively, e.g., under chirality transfer.[1] In this context, carbon-carbon, as well as carbon-heteroatom bond forming processes are of major interest, triggering the development of preparatively useful methods involving functionalized allenes, such as additions,[2] Diels–Alder reactions,[3] and palladium-catalyzed transformations.[4] Moreover, the increasing number of allenic pharmaceuticals[5] and natural products[1,6] highly stimulated the investigation of allenes in target-oriented synthesis.

In this account, we will summarize recent results of our own work on functionalized allenes and their use in the preparation of natural and non-natural products. Hence, the stereoselective synthesis of α-hydroxyallenes and their subsequent transformation into 2,5-dihydrofurans represent an example of allenes as potential building blocks in natural product synthesis, whereas the generation of allenic α-amino acid derivatives illustrates our interest in the formation of new pharmacologically active allenic compounds.

2 Synthesis of α-Allenic α-Amino Acids

In the course of our investigations on the synthesis of functionalized allenes via 1,6-addition of organocuprates to acceptor-substituted enynes,[7] we became particularly interested in allenic α-amino acid derivatives due to their potential biological activity. Allenic α-amino acids (as well as other unsaturated α-amino acids) act as specific mechanism-based inhibitors of vitamin B_6 linked decarboxylases.[8] In particular the introduction of an allenic entity into an α-amino acid enables the formation of a highly specific inhibitor with promising therapeutic utility through the additional incorporation of axial chirality into the molecule. But despite the fact that α-allenyl DOPA **1** rapidly inactivates porcine kidney aromatic group amino acid decarboxylase,[9] few attempts towards the synthesis of further α-allenic α-amino acids have been reported to date (Figure 1). Moreover, no natural α-allenic α-amino acid is known so far; the only example of a naturally occuring α-amino acid comprising an allenic moiety is the β-allenic amino acid **2**, which has been isolated from the mushroom *Amanita solitaria* and other *Amanita* species.[10] This unsaturated compound, however, shows only low biological activity.

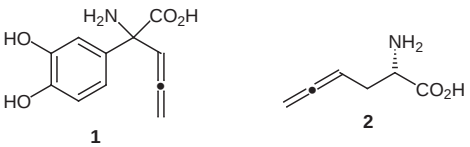

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Figure 1 Pharmacologically active and naturally occuring allenic amino acids.

Unfortunately, closer investigations of this interesting class of compounds as potential pharmaceuticals were hampered due to difficulties in their synthesis. In contrast to β- and γ-allenic α-amino acids, which are quite easily accessible via S_N2'-substitution of propargylic electro-

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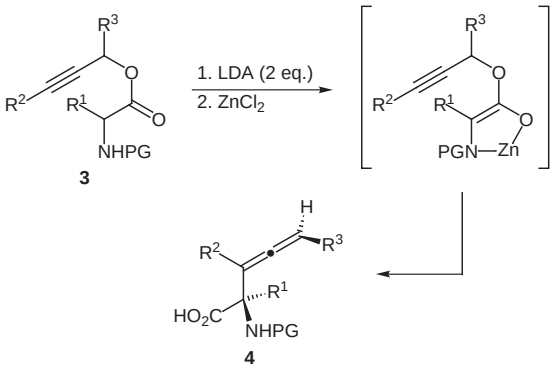
philes with amino acid derived organozinc reagents[11] and direct palladium-catalyzed allenylation,[12] respectively, the synthesis of α-allenic α-amino acids faces several problems. The most efficient approach towards the preparation of these unsaturated compounds relies upon [3,3]-sigmatropic rearrangement reactions. However, in the case of Ireland–Claisen rearrangements of propargylic amino esters **3**[13] only low chemical yields were obtained, whereas the chelate-controlled Claisen rearrangement of such amino esters[14] suffers from limitations regarding the substitution pattern. Due to steric hindrance in the transition state, only α-allenic α-amino acid derivatives **4** containing a small substituent at position C-5 are accessible via this route (Scheme 1).



Scheme 1 Synthesis of α-allenic α-amino acid derivatives **4** by chelate-controlled Claisen rearrangement.

Biographical Sketches

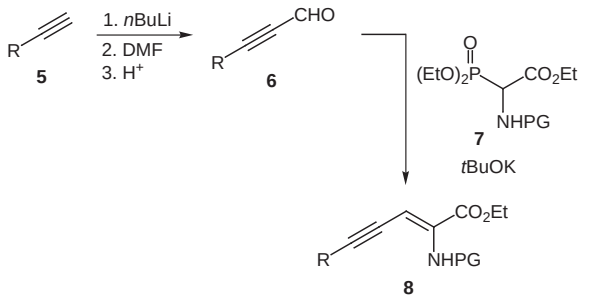
Norbert Krause (born 1959 in Wolfsburg, Germany) studied chemistry at the Technical University of Braunschweig and obtained his PhD degree in 1986 under the guidance of H. Hopf for research on sterically and electronically modified retinoids. After one-year postdoctoral appointments with D. Seebach (ETH Zürich, Switzerland) and M. Saunders (Yale University, New Haven, USA), he obtained his habilitation for organic chemistry in the group of K. Hafner at the Technical University of Darmstadt in 1993. He became associate professor at the University of Bonn in 1994 and full professor at the University of Dortmund in 1998. His research interests cover the development and mechanistic understanding of organometallic reactions, their application to the synthesis of natural and unnatural products, and stereoselective protonation reactions. This work was recognized through the award of the Heinz–Maier–Leibnitz prize (1991), the ADUC annual prize for lecturers (1993), and a Heisenberg scholarship (1994).

Anja Hoffmann-Röder (born 1972 in Bonn, Germany) became laboratory technician at the Degussa AG in 1994 and then studied chemistry at the University of Bonn. In 1999, she obtained her Diploma with a thesis on chiral allenophanes under the joint supervision of F. Vögtle and N. Krause. She then moved to the University of Dortmund and is currently working in N. Krause's group on her PhD thesis about the utilization of allenes for the synthesis of natural products and pharmaceutically active compounds. Her studies were recognized through stipends from the Studienstiftung des Deutschen Volkes and the Fritzter-Meer foundation, and by a PhD scholarship from the Stiftung Stipendien-Fonds des Verbandes der Chemischen Industrie. In 2001, she joined the groups of A. Alexakis (University of Geneva, Switzerland) and Y. Yamamoto (Tohoku University, Sendai, Japan) for scientific short-term missions, which were sponsored by the European Community and the Japanese Ministry of Education, Culture, Sports, Science and Technology (Monbukagakusho).

Johannes Canisius (born 1967 in Bonn, Germany) studied chemistry at the University of Bonn and obtained his Diploma in 1996 under the supervision of N. Krause. In 1998, he moved to the University of Dortmund and obtained his PhD degree in 2000 under the guidance of N. Krause for research on mechanistic and preparative aspects of copper-mediated Michael additions. He is now working as a research chemist at Witco Crompton Corp. (Bergkamen, Germany).

In order to overcome these limitations and to initiate further investigations on the structure-reactivity-relationship of these interesting bioactive compounds, we decided to develop a different strategy for the synthesis of α-allenic α-amino acids. Since the 1,6-addition of organocuprates to acceptor-substituted enynes has proven to be an efficient way for the synthesis of highly functionalized allenes,[7] we applied this method to protected amino enynoates **8**, thus leading to the formation of trisubstituted α-allenic α-amino acids **9**. Alternative approaches towards the introduction of an amino group into allenic esters either via electrophilic azidation[15] of the corresponding ester enolate or Mitsunobu reaction[16] of α-hydroxy allenic esters failed, furnishing the desired allenic azido esters only in minor amounts.[17]

2-En-4-ynoates can be easily prepared through Wittig–Horner–Wadsworth–Emmons (WHWE) reaction of acetylenic aldehydes with suitably functionalized phosphonates.[18] Extension of this method towards the synthesis of α-amino substituted enynoates **8** required protection of the amino functionality either as an amide or a carbamate (Scheme 2).[17,19]



Scheme 2 Synthesis of 2-amino-2-en-4-ynoates **8**.

The reaction sequence started with alkynes **5** which were formylated with *N*,*N*-dimethylformamide after deprotonation with butyllithium.[20] The resulting unsaturated aldehydes **6** proved to be unstable and were therefore subjected without purification to the following WHWE olefination. Thus, in the presence of the protected α-aminophosphonates **7** and potassium *tert*-butoxide as a base, the desired α-amino enynoates **8** were obtained in moderate to good chemical yields (Table 1).

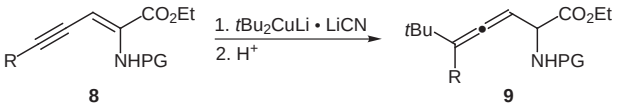
As outlined in Table 1, the reaction is not restricted to alkyl-substituted allenic amino esters, but tolerates beside alkenyl even aryl and trimethylsilyl substituents. Moreover, the WHWE reaction proceeds stereoselectively, furnishing the *Z*-configurated products exclusively. Only in the case of the doubly protected amino ester **8a**, the geometry of the double bond was found to be *E*, indicating a sterically induced preference for the intermediate oxaphosphetane with the triple bond being *trans* to the protected amino group. The geometry of the double bond of the amino esters was established by NMR-spectroscopy through determination of the $^3J_{C-H}$ coupling constants of the carbon resonance at C-1. Comparison of these data with the known enynoates ethyl (*E*)-6,6-dimethylhept-2-

Table 1 Synthesis of α-Amino Enynoates **8** and α-Allenic α-Amino Acids **9**

Entry	Enynoate	R	PG	Yield of **8** (%)	Configuration	Yield of **9** (%)
1	**8a**	*t*-Bu	Bz/Cbz[a]	42	*E*	0
2	**8b**	*t*-Bu	Boc	71	*Z*	71
3	**8c**	Ph	Boc	23	*Z*	54
4	**8d**	1-cyclohexenyl	Boc	60	*Z*	63
5	**8e**	Me_3Si	Boc	61	*Z*	68
6	**8f**	*t*-Bu	Ac	47	*Z*	42

[a] Nitrogen doubly protected.

en-4-ynoate[21] and ethyl (*Z*)-2-acetyl-amino-5-phenylpent-2-en-4-ynoate,[22] respectively, revealed large coupling constants of $^3J_{C-H}$ = 5.9–9.8 Hz for the *E*-configurated products, whereas the corresponding enynoates with *Z*-configuration of the double bond show coupling constants in the range of $^3J_{C-H}$ = 3.9–4.6 Hz. Additionally, the structures of the doubly protected amino ester **8a**[23] and its acetyl analogue **8f**[24] were confirmed by X-ray analysis.

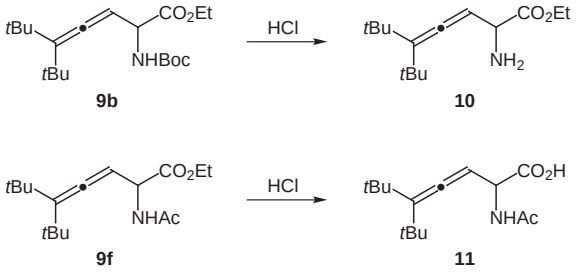


Scheme 3 Synthesis of α-allenic α-amino acid derivatives **9** by 1,6-cuprate addition.

The subsequent transformations to the allenic amino esters **9** were achieved with an excess of lithium *tert*-butylcyanocuprate (*t*-$Bu_2CuLi{\cdot}LiCN$) in Et_2O (Scheme 3, Table 1); the doubly protected amino ester **8a**, however, did not react under these conditions. Also, less reactive organocuprates such as $Me_2CuLi{\cdot}LiCN$, $Me_2CuLi{\cdot}LiI$ or $Ph_2CuLi{\cdot}LiCN$ did not furnish any reaction product at all, even in the presence of different Lewis acids as additives (e.g., Me_3SiOTf) or a higher cuprate-to-substrate ratio. By contrast, the use of the *tert*-butylcyanocuprate enables the preparation of even sterically encumbered allenic esters in moderate to good chemical yields and as a mixture of both diastereomeric products, due to a nonselective protonation of the allenyl enolate formed during the 1,6-addition.[25]

Last but not least, acidic treatment of the Boc-protected amino ester **9b** with hydrochloric acid (6 M) resulted in a chemoselective cleavage of the *N*-butoxycarbonyl group, furnishing the corresponding α-allenic α-amino ester **10** in 87% yield. Contrarily, in the case of the acetyl-protected amino ester **9f** the ester group instead of the amino-pro-

tecting group was cleaved, thus providing the *N*-protected amino acid **11** (66% yield, Scheme 4).

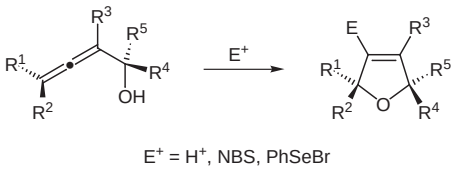


Scheme 4 Selective deprotection of α-allenic α-amino acid derivatives **9b**/**f**.

In summary, we have shown that the 1,6-addition of organocuprates to amino-substituted enynoates **8** represents an attractive alternative for the preparation of α-allenic α-amino acid derivatives. The reaction sequence outlined above not only furnishes the desired *tert*-butyl-substituted amino ester derivatives **9**, **10**, and **11**, respectively, but also allows for the introduction of sterically demanding substituents at the allenic moiety.

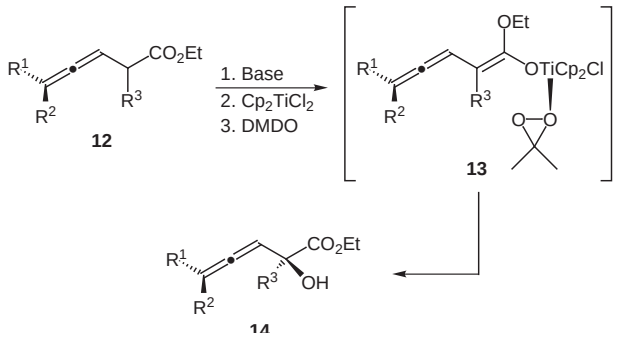
3 Synthesis of 2,5-Dihydrofurans

Besides, the above mentioned amino-functionalized allenes, α-hydroxyallenes have also proven to be highly rewarding as building blocks in natural product synthesis. In this context, we became particularly interested in the electrophilically induced cyclization of these compounds to 2,5-dihydrofurans[26] since the latter represent pivotal structural elements of a wide variety of different biologically active molecules. For instance, 2,5-dihydrofurans can be found in mycotoxins,[27] polyether antibiotics,[28] spiroketals,[29] and even amino acids.[30] The generation of these heterocycles from allenic precursors not only benefits from the high reactivity of α-hydroxyallenes but also from their inherent axial chirality, which allows the cyclization to proceed stereoselectively under chirality transfer (Scheme 5).



Scheme 5 Electrophilically induced cyclization of α-hydroxyallenes to 2,5-dihydrofurans.

The required α-hydroxyallenes are mainly accessible by S_N2'-ring opening reaction of propargylic epoxides with organometallic compounds[31] or via oxidation of in situ formed enolates of 3,4-dienoates.[32] In the latter case, allenic esters **12**, which are again provided through the above outlined 1,6-addition of organocuprates to enynoates,[7] were (after deprotonation) transformed into the corresponding titanium ester enolates[33] and reacted with dimethyl dioxirane (DMDO) in acetone following Adam's protocol.[34] The resulting α-hydroxy allenic esters **14** were obtained in variable yields and diastereoselectivities depending upon the substitution pattern of the parent allene (Scheme 6, Table 2).



Scheme 6 Synthesis of 2-hydroxy-3,4-dienoates **14** by enolate oxidation with DMDO.

Table 2 Oxidation of 3,4-Dienoates **12** to α-Hydroxyallenes **14**

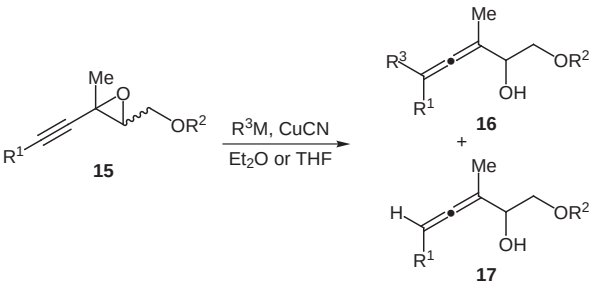
Entry	Enynoate	R^1	R^2	R^3	Base	Consumption of **12** (%)	Yield of **14** (%)[a]	ds
1	**12a**	*t*-Bu	Me	H	LDA	46	68	90:10
2	**12b**	*t*-Bu	Me	Me	LDA	19	63	80:20
3	**12b**	*t*-Bu	Me	Me	LHMDS	32	75	80:20
4	**12c**	*t*-Bu	*n*-Bu	H	LDA	55	67	60:40
5	**12c**	*t*-Bu	*n*-Bu	H	LHMDS	53	99	60:40
6	**12d**	*n*-Bu	*n*-Hex	H	LDA	63	87	50:50
7	**12e**	*t*-Bu	*n*-Hex	Me	LDA	30	56	60:40

[a] With respect to consumed starting material **12**.

In the enolate oxidation reactions examined here, no complete conversion of the starting allenic ester **12** was observed, even with a large excess of DMDO. Presumably, the desired oxidation is competing with the protonation of the enolate by acetone, which (as a result of the DMDO preparation) is present in the reaction mixture in large amounts. Besides, the dioxirane may react with the conjugate acid of the base used for the deprotonation of the ester (i.e., diisopropylamine), resulting in the decomposition of the oxidizing agent.[34] In this regard, it is noteworthy that the use of lithium hexamethyldisilazide as a base instead of LDA led to increased comsumption of substrate **12b**.[35] Interestingly, in the case of allene **12c** an unchanged conversion but a much higher yield were observed, indicating less side reactions. Generally, substrate conversions in the range of 20–30% were found with allenes bearing a methyl group at C-2 (Table 2, entries 2,3,7), whereas substrates without a substituent in this position gave ca 50–60% conversion.

The highest diastereoselectivities (of up to 90% in the case of allene **12a**, entry 1) were obtained with 3,4-dienoates bearing substituents of different size at C-5, presumably due to complexation of the DMDO to the titanium enolate and subsequent oxygen transfer from the less shielded diastereotopic side [cf. possible intermediate **13**; the deprotonation of 3,4-dienoates with LDA is known to produce the *E*(OLi)-enolates selectively[7]]. The relative configuration of the major diastereomer was determined by cyclization to the corresponding 2,5-dihydrofuran (vide infra).[32] However, introduction of an additional substituent at C-2 lowered the diastereoselectivity of the oxidation reaction (Table 2, entries 2,3,7). The same trend was observed with allenes bearing longer alkyl chains at C-5 (Table 2, entries 4–7); in the case of substrate **12d** (Table 2, entry 6), no diastereoselectivity is expected since the alkyl groups at C-5 are virtually of the same size.

The alternative route for generation of α-hydroxyallenes via S_N2'-substitution reaction of propargylic epoxides **15** with stoichiometric amounts of organocuprates at –20 °C proceeded smoothly in the case of *t*-$Bu_2CuLi{\cdot}LiCN$ furnishing the desired allenic alcohols **16a**,**b** in good chemical yields (Scheme 7; Table 3, entries 1,2). Similarly, treatment of oxirane *cis*-**15a** with *n*-$Hex_2CuLi{\cdot}LiCN$ (Table 3, entry 3) gave the desired substitution product **16c**, which was contaminated with 15% of the (formal) reduction product **17a**. The formation of products of this type has been observed previously and was attributed to the protonation of a rather stable copper intermediate during work-up.[26f] In this reaction, the presence of tri-*n*-butylphosphine served to improve the ratio of substitution to (formal) reduction.



Scheme 7 Synthesis of α-hydroxyallenes **16**,**17** from propargylic epoxides **15**

Contrarily, the (formal) reduction product **17** was obtained as the major product in the corresponding reaction of *cis*- or *trans*-**15a** with $Me_2CuLi{\cdot}LiCN$, and this situation could neither be improved by changing the solvent from Et_2O to THF nor through addition of an alkylating agent such as methyl iodide[26f] prior to work-up. Fortunately, addition of *n*-Bu_3P led again to the predominant formation of the desired substitution product **16d** with high diastereoselectivity (entry 4). The corresponding reaction with Grignard reagents in the presence of stoichiometric amounts of CuCN gave similar results, although sometimes direct nucleophilic substitution of the epoxide occured as a side reaction (in particular if the reaction was

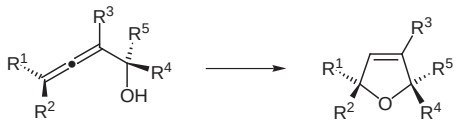
Table 3 Nucleophilic Ring Opening of Propargyl Oxiranes **15**

Entry	Substrate	R^1	R^2	R^3M	Additive	Major Product	Ratio **16**:**17**	Yield (%)[a]	ds of **16**
1	*trans*-**15a**	H	TBS	*t*-BuLi	*n*-Bu_3P	**16a**	100:0	66	65:35
2	*trans*-**15b**	Me	Me	*t*-BuLi	$(EtO)_3P$	**16b**	100:0	66	80:20
3	*cis*-**15a**	H	TBS	*n*-HexLi	*n*-Bu_3P	**16c**	85:15	77	75:25
4	*cis*-**15a**	H	TBS	MeLi	*n*-Bu_3P	**16d**	94:6	77	85:15
5	*cis*-**15a**	H	TBS	MeMgBr	*n*-Bu_3P	**16d**	100:0	70	94:6
6	*trans*-**15a**	H	TBS	MeLi	–[b]	**17a**	20:80	87	–
7	*trans*-**15b**	Me	Me	MeLi	–[b]	**16e**	90:10	80	–

[a] Combined yield of **16** and **17**.
[b] Reaction carried out at –80 °C.

run under copper catalysis[31a] according to Alexakis' protocol). Thus, treatment of the silylated epoxide *cis*-**15a** with the magnesium cuprate $Me_2CuMg_2(CN)Br_2$ furnished the desired hydroxyallene with good chemical yield and diastereoselectivity (entry 5). Last but not least, the formal reduction product was obtained predominantly by treating *trans*-**15a** with the cyanocuprate $Me_2CuLi{\cdot}LiCN$ at low temperature (–80 °C) in the absence of any additive, resulting in the formation of an 80:20-mixture of products **17a** and **16d**. Unfortunately, the corresponding reaction of the propargylic oxirane *trans*-**15b** (which bears a methyl group at the triple bond) demonstrates that this behavior is substrate-dependent: in this case a 90:10 ratio of substitution vs. (formal) reduction was observed (entry 7).

All α-hydroxyallenes **14** and **16**, obtained either via ester enolate oxidation or via S_N2'-substitution reaction, were smoothly converted into the corresponding 2,5-dihydrofurans **18** under complete axis to center chirality transfer (Scheme 8; Table 4). Whereas the 2-hydroxy-3,4-dienoates **14** were easily cyclized upon treatment with hydrogen chloride gas in chloroform or, more conveniently, by using acidic Amberlyst 15 resin in refluxing dichloromethane, the silylated hydroxyallenes **16** required milder reaction conditions. Hence, such acid labile substrates (or those which would readily undergo elimination due to steric hindrance) were efficiently transformed using 5 to 10 mol-% of gold(III)-chloride as a catalyst.[36] Again, as in the acid-induced cyclizations, the reaction not only proceeded under complete chirality transfer, but also proved to be of wide scope with regard to the substitution pattern of the allenic entity, furnishing both, tri- and tetrasubstituted 2,5-dihydrofurans in good to excellent chemical



14/16/17 **18**

Scheme 8 Cyclization of α-hydroxyallenes **14**,**16**,**17** to 2,5-dihydrofurans **18**.

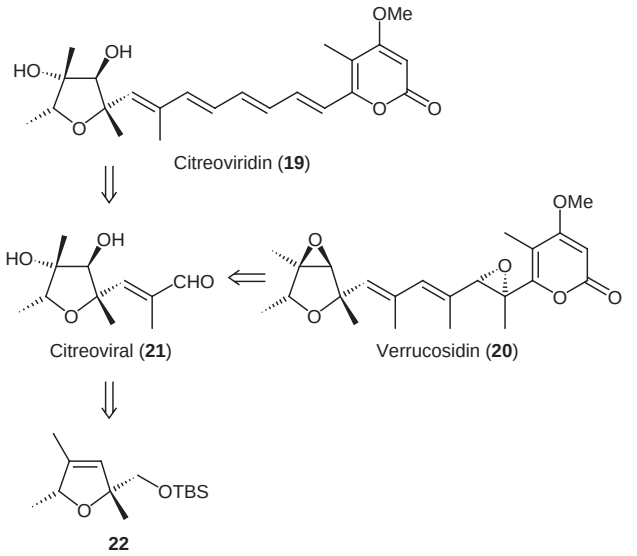
yields. The relative configurations of the major diastereomers of dihydrofurans **18a** and **18h**, respectively, were determined with the aid of NOE experiments,[32,36] confirming also those of the corresponding α-hydroxyallenes.

With these mild and efficient cyclization methods in hand, we searched for their application in natural product synthesis. In this respect, the functionalized aldehyde citreoviral (**21**),[37] which is a key intermediate in the synthesis of two structural related antiparasitic mycotoxins, citreo-viridin (**19**)[27a] and verrucosidin (**20**),[27b] represents a promising target molecule (Scheme 9). In particular, citreoviridin (**19**), isolated from *Penicillium citreoviride*, has gained further interest as a potent neurotoxin, due to its highly specific inhibition of mitochondrial F_1,F_0-ATPase causing cardiac Beriberi disease.[38]

These intriguing physiological properties have attracted several synthetic approaches towards the total synthesis of citreoviridin (**19**) and its metabolite citreoviral (**21**),[39,40] which is far less toxic. While most of these syntheses required rather long multistep reaction sequences starting from precursors of the 'chiral pool', such as carbohydrates,[41] glycerinaldehyde,[42] or lactate,[43] Marshall's group reported a formal synthesis using an α-hydroxyal-

Table 4 Cyclization of Hydroxyallenes **14** and **16** to 2,5-Dihydrofurans **18**

Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Reagent	Product	Yield of **18** (%)	ds
1	**14a**	*t*-Bu	Me	H	CO_2Et	H	HCl	**18a**	90	90:10
2	**14a**	*t*-Bu	Me	H	CO_2Et	H	Amberlyst 15	**18a**	quant.	90:10
3	**14a**	*t*-Bu	Me	H	CO_2Et	H	$AuCl_3$	**18a**	74	90:10
4	**14b**	*t*-Bu	Me	H	CO_2Et	Me	HCl	**18b**	92	80:20
5	**14c**	*t*-Bu	*n*-Bu	H	CO_2Et	H	HCl	**18c**	80	60:40
6	**14c**	*t*-Bu	*n*-Bu	H	CO_2Et	H	$AuCl_3$	**18c**	quant.	60:40
7	**14d**	*n*-Bu	*n*-Hex	H	CO_2Et	H	HCl	**18d**	90	50:50
8	**16a**	*t*-Bu	H	Me	CH_2OTBS	H	$AuCl_3$	**18e**	95	65:35
9	**16b**	*t*-Bu	Me	Me	CH_2OMe	H	$AuCl_3$	**18f**	90	80:20
10	**16c**	H	*n*-Hex	Me	CH_2OTBS	H	$AuCl_3$	**18g**	65	75:25
11	**16d**	H	Me	Me	CH_2OTBS	H	$AuCl_3$	**18h**	77	94:6
12	**17a**	H	H	Me	CH_2OTBS	H	$AuCl_3$	**18i**	86	–



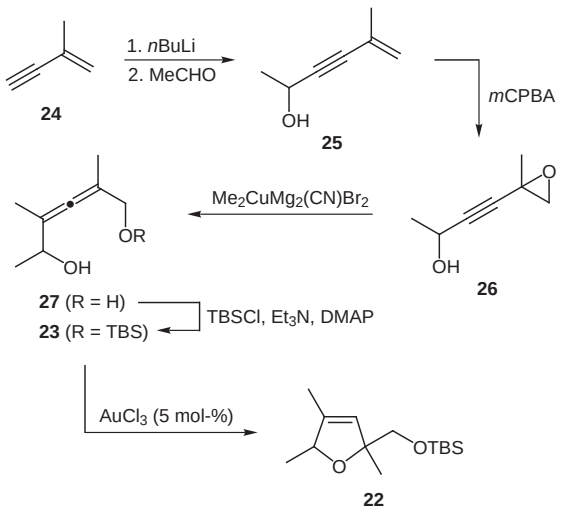
Scheme 9 Retrosynthesis of mycotoxins citreoviridin (**19**) and verrucosidin (**20**) via citreoviral (**21**).

lene for the stereoselective construction of the 2,5-dihydrofuran core.[26f] Nevertheless, this approach still covered 9 steps and relied in its key reaction upon a heterogeneous Ag(I)-induced cyclization of hydroxyallene **23** to the citreoviral precursor **22** (Scheme 10). Here, almost stoichiometric amounts of silver nitrate were required to achieve a good yield of product **22**.

Scheme 10 Silver-promoted cyclization of α-hydroxyallene **23** to 2,5-dihydrofuran **22**.[26f]

Thus, based on our own work on the use of α-hydroxyallenes as synthetic intermediates, we were able not only to present an efficient and considerably shorter access to **22**, but also to improve the key step of the synthesis by employing our new gold-catalyzed cyclization method. Moreover, our route opens up a convenient access to a variety of structural analogues of citreoviral (**21**) for further investigations on the structure-reactivity-relationship of this type of compounds.

The reaction sequence started with enyne **25**, easily accessible via addition of the lithium acetylide of 2-methylbut-1-en-3-yne (**24**) to acetaldehyde,[44] which after epoxidation with *m*CPBA furnished **26** in 58% chemical yield as a 60:40 mixture of diastereomers (Scheme 11). About the same yield and selectivity were observed when DMDO[34a] was employed as epoxidation agent. The resulting epoxide **26** was then subjected to a S_N2'-substitution reaction with 2 equivalents of the magnesium cyanocuprate $Me_2CuMg_2(CN)Br_2$ in Et_2O. In this case, clean formation



Scheme 11 Synthesis of 2,5-dihydrofuran **22** via propargylic epoxide **26**

of the desired allene was observed, thus furnishing diol **27** after column chromatography in 43% chemical yield. Finally, selective protection of the primary hydroxyl group as a TBS-ether provided α-hydroxyallene **23**, which was then converted into the dihydrofuran **22** upon treatment with 5 mol-% $AuCl_3$ in dichloromethane (80% yield). Compared to Marshall's Ag(I)-promoted cyclization, gold(III)-catalysis here proved to be particularly advantageous not only for economical and ecological reasons but also in terms of reactivity. Thus, complete conversion of hydroxyallene **23** was achieved in 3 hours at room temperature, furnishing the spectroscopically pure cyclization product **22** after removal of the catalyst in 80% chemical yield as a 60:40 mixture of diastereomers. Subsequent steps for the transformation of **22** into racemic citreoviral (**21**) follow the route outlined in Marshall's work.[26f]

In summary, we present a new route to α-hydroxyallenes via oxidation of allenic ester enolates with DMDO and their conversion into functionalized 2,5-dihydrofurans upon acid-induced cyclization. Furthermore, we developed a stereoselective and efficient cyclization method for α-hydroxyallenes bearing acid-sensitive functionalities by making use of gold(III)-catalysis. The latter protocol proved to be advantageous compared to the well-known stoichiometric cyclization procedures due to its mildness and reactivity, and last but not least, was successfully applied to a short and concise synthesis of 2,5-dihydrofuran **22**, a versatile precursor for *rac*-citreoviral (**21**). A diastereo- and enantioselective synthesis of citreoviral via this route is currently under investigation in our laboratories.

4 Conclusion

In this account, we demonstrated the versatility of functionalized allenes as potent building blocks in target-oriented synthesis, benefitting from their unique reactivity and chirality. In this respect, we presented at first an im-

proved access to substituted α-allenic α-amino acids, an interesting class of pharmacologically active allenes which may act as inhibitors of vitamin B_6 decarboxylases. The formation of α-allenic α-amino acid derivatives through 1,6-addition reaction of organocuprates to amino-substituted enynoates thereby allowed the generation of even sterically encumbered representatives. Such promising target molecules for investigations of structure-reactivity-relationships were not accessible by traditional methods. In the second part, we demonstrated that α-hydroxyallenes are also highly useful synthetic tools in natural product synthesis. These molecules can be again obtained in an elegant way using a 1,6-cuprate addition-oxidation sequence or by copper-promoted S_N2'-substitution reaction of propargylic oxiranes. Subsequent acid-induced or gold(III)-catalyzed cyclization to the corresponding 2,5-dihydrofurans (which are common structural elements in a wide variety of natural products) enabled the generation of these heterocycles in a highly stereoselective mode. The efficiency of this new cyclization protocol was illustrated in a short formal synthesis of racemic citreoviral. In the future, we will work on the extension of this method to the synthesis of other dihydrofuran-based natural products, as well as on the generation of further pharmacologically active allenic compounds.

NMR spectra were recorded with a Bruker WM 400 spectrometer at 400 MHz (^{1}H) and 100.6 MHz (^{13}C) in $CDCl_3$ as solvent and internal standard (δ = 7.27 for ^{1}H, δ = 77.05 for ^{13}C). The signals of the major component of a product mixture are marked with an asterisk (*). IR spectra were obtained with a Perkin-Elmer 1600 FT-IR spectrometer, mass spectra with Finnigan MAT 8230 (EI, 70 eV), Thermoquest TSQ API (ESI), or JEOL SX102A (FAB) spectrometers. GC-MS spectra were recorded with a Finnigan ITD 800 and a Finnigan Polaris GCQ spectrometer. GC analyses were carried out with a Carlo Erba GC 8000 gas chromatograph with helium as the carrier gas and an OV-1701 capillary column. Elemental analyses were obtained with Perkin Elmer CHN 240 A and B analyzers. The reactions were carried out in thoroughly dried glassware under argon. Et_2O was distilled from $LiAlH_4$ prior to use. BuLi, *t*-BuLi and *n*-HexLi were titrated with diphenylacetic acid according to the procedure of Kofron and Baclawski.[45]

Some α-hydroxyallenes and 2,5-dihydrofurans were too unstable to obtain correct elemental analyses or high-resolution mass spectra.

Preparation of 2-Amino-substituted Enynoates 8; General Procedure[17,20]

To a soln of alkyne **5** (1.1 equiv) in Et_2O was added at –40 °C *n*-BuLi (hexane soln, 1 equiv). After addition of anhyd DMF (1.2 equiv), the mixture was warmed to r.t.and stirred for 30 min; it was then added to a vigorously stirred mixture, cooled to 5 °C, of 10% aqueous NaH_2PO_4 soln and Et_2O (5 mL each/mmol **5**). The phases were separated and the aqueous layer was washed with Et_2O. The combined organic phases were dried with $MgSO_4$, and the major part of the solvent was distilled off under ambient pressure. The crude aldehyde **6** was used without purification in the next step.

A suspension of *t*-BuOK (1 equiv) in CH_2Cl_2 was cooled to –78 °C, a soln of phosphonate **7** in CH_2Cl_2 was added dropwise. After stirring for 30 min at –78 °C, a soln of the crude aldehyde **5** (1 equiv) in THF (1 mL/mmol **5**) was added dropwise, and the mixture was stirred for 1 h at –78 °C. After hydrolysis, the layers were separated and the aqueous phase was washed with Et_2O. The combined organic layers were washed with H_2O and dried with $MgSO_4$; the solvent was removed in vacuo, and the crude product was purified by crystallization or column chromatography.

Ethyl *(E)*-2-[benzyl-(benzyloxycarbonyl)amino]-6,6-dimethylhept-2-en-4-ynoate (8a):

3,3-Dimethylbutyne (287 mg, 3.5 mmol), in Et_2O (10 mL), *n*-BuLi (1.5 M in hexane; 2.1 mL, 3.2 mmol), DMF (0.36 mL, 4.4 mmol), *t*-BuOK (336 mg, 3.0 mmol) in CH_2Cl_2 (5 mL), and ethyl 2-[benzyl-(benzyloxycarbonyl)-amino]-2-(diethoxyphosphoryl)-acetate (1.39 g, 3.0 mmol) [46] in CH_2Cl_2 (5 mL). Purification of the crude product by column chromatography (SiO_2; cyclohexane–Et_2O, 10:1) furnished **8a** (542 mg, 43%) as colorless needles; mp 89 °C.

IR (KBr): 2970 (s, C–H), 2195 (s, C≡C), 1720 (s, C=O), 1612 cm^{-1} (s, C=C).

^{1}H NMR ($CDCl_3$): δ = 7.34–7.28 (m, 10 H, Ph), 5.81 (s, 1 H, 3-H), 5.19 (s, 2 H, NCH_2Ph), 4.77 (s, 2 H OCH_2Ph), 4.15–4.02 (m, 2 H, CH_2CH$_3$), 1.26 [s, 9 H, C(CH$_3$)$_3$], 1.25–1.05 (m, 3 H, CH$_2$CH_3).

^{13}C NMR ($CDCl_3$): δ = 163.8 (C-1), 155.6 (NCO), 137.6 (C-4), 136.4 (C-2), 129.0, 128.8, 128.5, 127.8 (4+, Ph), 115.5 (+, C-3), 111.1 (C-5), 77.5 (C-4), 68.4 (–, OCH$_2$Ph), 61.6 (–, *C*H$_2$CH$_3$), 54.5 (–, NCH$_2$Ph), 30.9 [+, C(*C*H$_3$)$_3$], 28.9 (C-6), 14.5 (+, CH$_2$*C*H$_3$).

MS (EI): *m*/*z* (%) = 419 (15, M$^+$), 328 (70), 284 (70), 91 (100).

Anal. Calcd for $C_{26}H_{29}NO_4$ (419.53): C, 74.44; H, 6.97; N, 3.34. Found: C, 74.30; H, 7.00; N, 3.30.

Ethyl (*Z*)-2-[(*t*-Butoxycarbonyl)amino]-6,6-dimethylhept-2-en-4-ynoate (8b)

3,3-Dimethylbutyne (3.83 g, 46.7 mmol) in Et_2O (45 mL), *n*-BuLi (2.0 M in hexane; 21.0 mL, 42.0 mmol), DMF (4.3 mL ,56.0 mmol), *t*-BuOK (3.98 g, 35.5 mmol) in CH_2Cl_2 (70 mL) and ethyl 2-[(*t*-butoxycarbonyl)amino]-2-(diethoxyphosphoryl)-acetate (12.03 g, 35.5 mmol) [47] in CH_2Cl_2 (50 mL). Purification of the crude product by column chromatography (SiO_2; cyclohexane–Et_2O, 10:1) furnished **8b** (7.43 g, 71%) as colorless needles; mp 72 °C.

IR (KBr): 3241 (s), 3212 (s, N–H), 2932 (s, C–H), 2194 (s, C≡C), 1724 (s, C=O), 1722 (s, C=O), 1616 (s, C=C), 1470 cm^{-1} (s, N–H).

^{1}H NMR ($CDCl_3$): δ = 6.32 (s, 1 H, NH), 6.00 (s, 1 H, 3-H), 4.20 (q, *J* = 7.3 Hz, 2 H, CH$_2$), 1.49 [s, 9 H, OC(CH$_3$)$_3$], 1.25 (t, 3 H, *J* = 7.3 Hz, CH$_2$CH_3), 1.22 [s, 9 H, CC(CH$_3$)$_3$].

^{13}C NMR ($CDCl_3$): δ = 164.0 (C-1), 151.8 [(CH$_3$)$_3$CO*C*], 134.6 (C-2), 112.7 (C-5), 106.9 (+, C-3), 80.9 [O*C*(CH$_3$)$_3$], 73.8 (C-4), 61.5 (–, CH$_2$), 30.7 (+, CC(*C*H$_3$)$_3$), 28.5 (C-6), 28.0 (+, OC(*C*H$_3$)$_3$), 14.0 (+, CH$_2$*C*H$_3$).

MS (EI): *m*/*z* (%): 295 (14, M$^+$), 195 (100), 180 (49), 166 (26).

Anal. Calcd for $C_{16}H_{25}NO_4$ (295.38): C, 65.06; H, 8.53; N, 4.74. Found: C, 65.00; H, 8.40; N, 4.70.

Ethyl (*Z*)-2-[(*t*-Butoxycarbonyl)amino]-5-phenylpent-2-en-4-ynoate (8c)

Phenylacetylene (1.33 g, 13.0 mmol) in Et_2O (15 mL) , *n*-BuLi (2.0 M in hexane; 5.9 mL, 11.7 mmol), DMF (1.2 mL, 15.6 mmol), *t*-BuOK (1.12 g, 10.0 mmol) in CH_2Cl_2 (20 mL), and ethyl 2-[(*t*-butoxycarbonyl)amino]-2-(diethoxyphosphoryl)-acetate (3.38 g, 10.0 mmol)[47] in CH_2Cl_2 (15 mL). Crystallization of the crude product from hexane furnished **8c** (737 mg, 23%) as slightly brown needles (mp 95 °C).

IR (KBr): 3227 (s, N–H), 2932 (s, C–H), 2200 (s, C≡C), 1722 (s, C=O), 1708 (s, C=O), 1623 (s, C=C), 1477 cm^{-1} (s, N–H).

^{1}H NMR ($CDCl_3$): δ = 7.36–7.21 (m, 5 H, Ph), 6.54 (br s, 1 H, NH), 6.17 (s, 1 H, 3-H), 4.17 (q, 2 H, *J* = 7.0 Hz, CH$_2$), 1.38 [s, 9 H, C(CH$_3$)$_3$], 1.21 (t, 3 H, J = 7.0 Hz, CH$_2$CH_3).

^{13}C NMR ($CDCl_3$): δ = 163.8 (C-1), 151.7 [$(CH_3)_3COC$], 135.6 (C-2), 131.6, 128.9, 128.3 (3+, Ph), 122.5 (Ph), 105.5 (+, C-3), 102.3 (C-5), 84.1 (C-4), 81.1 [$C(CH_3)_3$], 61.8 (–, CH_2), 28.0 [+, $C(CH_3)_3$], 14.0 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 315 (16, M^+), 259 (9), 215 (19), 57 (100).

Anal. Calcd for $C_{18}H_{21}NO_4$ (315.37): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.60; H, 6.70; N, 4.40.

Ethyl (*Z*)-2-[(*t*-Butoxycarbonyl)amino]-5-(cyclohex-1-en-1-yl)-pent-2-en-4-ynoate (8d)

1-Ethynylcyclohexene (1.38 g, 13.0 mmol) in Et_2O (15 mL), *n*-BuLi (2.0 M in hexane; 5.9 mL, 11.7 mmol), DMF (1.2 mL, 15.6 mmol), *t*-BuOK (1.12 g, 10.0 mmol) in CH_2Cl_2 (20 mL), and ethyl 2-[(*t*-butoxycarbonyl)amino]-2-(diethoxyphosphoryl)-acetate (3.38 g, 10.0 mmol)[47] in CH_2Cl_2 (15 mL). Purification of the crude product by column chromatography (SiO_2; cyclohexane–Et_2O, 10:1) furnished **8d** (1.90 g, 60%) as a red oil.

IR (neat): 3334 (s, N–H), 2979 (s), 2934 (s, C–H), 2184 (s, C≡C), 1727 (s, C=O), 1708 (s, C=O), 1631 (s), 1609 (s, C=C), 1481 cm^{-1} (s, N–H).

^{1}H NMR ($CDCl_3$): δ = 6.40 (br s, 1 H, NH), 6.19 (m, 1 H, 2′-H), 6.15 (s, 1 H, 3-H), 4.24 (q, 2 H, *J* = 7.3 Hz, CH_2), 2.15–2.11 (m, 4 H, 3′-H, 6′-H), 1.65–1.56 (m, 4 H, 4′-H, 5′-H), 1.46 [s, 9 H, $C(CH_3)_3$], 1.28 (t, 3 H, *J* = 7.3 Hz, CH_2CH_3).

^{13}C NMR ($CDCl_3$): δ = 164.0 (C-1), 151.8 [$(CH_3)_3COC$], 137.2 (+, C-2′), 134.3 (C-2), 120.6 (C-1′), 106.5 (+, C-3), 104.8 (C-5), 81.7 (C-4), 81.1 [$C(CH_3)_3$], 61.7 (–, CH_2), 28.9, 25.9 (2 –, C-3′, C-6′), 28.1 [+, $C(CH_3)_3$], 22.1, 21.3 (2 –, C-4′, C-5′), 14.1 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 319 (46, M^+), 263 (15), 219 (38), 57 (100).

Anal. Calcd for $C_{18}H_{25}NO_4$ (319.40): C, 67.69; H, 7.89; N, 4.39. Found: C, 67.60; H, 7.90; N, 4.30.

Ethyl (*Z*)-2-[(*t*-Butoxycarbonyl)amino]-5-trimethylsilylpent-2-en-4-ynoate (8e)

Trimethylsilylacetylene (1.28 g, 13.0 mmol) in Et_2O (15 mL), *n*-BuLi (2.0 M in hexane; 5.9 mL, 11.7 mmol), DMF (1.2 mL, 15.6 mmol), *t*-BuOK (1.12 g, 10.0 mmol) in CH_2Cl_2 (20 mL), and ethyl 2-[(*t*-butoxycarbonyl)amino]-2-(diethoxyphosphoryl)-acetate (3.38 g, 10.0 mmol)[47] in CH_2Cl_2 (15 mL). Purification of the crude product by column chromatography (SiO_2; cyclohexane–Et_2O, 10:1) and crystallization from hexane furnished **8e** (1.90 g, 61%) as colorless needles; mp 85 °C.

IR (KBr): 3231 (s, N–H), 2977 (s), 2964 (s, C–H), 2129 (s, C≡C), 1731 (s, C=O), 1711 (s, C=O), 1639 (s, C=C), 1477 cm^{-1} (s, N–H).

^{1}H NMR ($CDCl_3$): δ = 6.45 (br s, 1 H, NH), 5.95 (s, 1 H, 3-H), 4.25 (q, 2 H, *J* = 7.0 Hz, CH_2), 1.47 [s, 9 H, $C(CH_3)_3$], 1.29 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 0.20 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 163.8 (C-1), 151.6 [$(CH_3)_3COC$], 136.8 (C-2), 108.8 (C-5), 104.4 (+, C-3), 98.9 (C-4), 81.4 [$C(CH_3)_3$], 61.8 (–, CH_2), 28.1 [+, $C(CH_3)_3$], 14.1 (+, CH_2CH_3), –0.2 [+, $Si(CH_3)_3$].

MS (EI): *m*/*z* (%) = 311 (15, M^+), 255 (7), 211 (100), 196 (23), 103 (35).

Anal. Calcd for $C_{15}H_{25}NO_4Si$ (311.46): C, 57.85; H, 8.09; N, 4.50. Found: C, 57.90, H, 8.00, N, 4.50.

Ethyl (*Z*)-2-(Acetylamino)-6,6-dimethylhept-2-en-4-ynoate (8f)

3,3-Dimethylbutyne (2.92 g, 35.6 mmol) in Et_2O (40 mL), *n*-BuLi (2.3 M in hexane;13.9 mL, 32.0 mmol), DMF (3.3 mL, 43.0 mmol), *t*-BuOK (2.99 g, 26.7 mmol) in CH_2Cl_2 (50 mL), and ethyl 2-(acetylamino)-2-(diethoxyphosphoryl)-acetate (7.50 g, 26.7 mmol)[47] in CH_2Cl_2 (40 mL). Crystallization of the crude product from hexane furnished (2.97 g, 47%) **8f** as colorless needles; mp 128 °C.

IR (KBr): 3212 (s), 3175 (s, N–H), 2970 (s, C–H), 2180 (s, C≡C), 1720 (s, C=O), 1680 (s, C=O), 1610 (s, C=C), 1529 cm^{-1} (s, N–H).

^{1}H NMR ($CDCl_3$): δ = 7.33 (br s, 1 H, NH), 6.18 (s, 1 H, 3-H), 4.17 (q, 2 H, *J* = 7.3 Hz, CH_2), 2.03 (s, 3 H, CH_3CO), 1.22–1.17 [m, 12 H, CH_2CH_3, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 168.1 (CH_3CO), 163.7 (C-1), 134.6 (C-2), 114.1 (C-5), 110.9 (+, C-3), 74.5 (C-4), 61.5 (–, CH_2), 30.5 [+, $C(CH_3)_3$], 28.5 [$C(CH_3)_3$], 22.8 (+, CH_3CO), 13.9 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 237 (30, M^+), 195 (12), 180 (100), 166 (48).

Anal. Calcd for $C_{13}H_{19}NO_3$ (237.30): C, 65.80; H, 8.07; N, 5.90. Found: C, 65.70; H, 8.00; N, 5.90.

1,6-Addition of *t*-Bu_2CuLi·LiCN to 2-Amino-substituted Enynoates; General Procedure

To a suspension of CuCN (2–4 equiv) in Et_2O was added at –30 °C *t*-BuLi (4–8 equiv) in pentane. After stirring for 15 min at –30 °C, a soln of Michael acceptor **8** (1 equiv) in Et_2O was added, and the mixture was stirred for 2 h at –10 °C. Then, a sat. aq NH_4Cl soln was added, and the mixture was filtered through Celite. The solvent was removed in vacuo, and the crude product purified by column chromatography (SiO_2; cyclohexane–Et_2O, 1:1-10:1).

Ethyl 2-[(*t*-butoxycarbonyl)amino]-5-*t*-butyl-6,6-dimethylhepta-3,4-dienoate (9b)

CuCN (1.78 g, 20.0 mmol) in Et_2O (50 mL), *t*-BuLi (1.5 M in pentane; 26.7 mL, 40.0 mmol), and **8b** (1.50 g, 5.0 mmol) in Et_2O (25 mL) furnished **9b** (1.25 g, 71%) as a yellow oil.

IR (KBr): 3448 (s, N–H), 2972 (s), 2908 (s), 2871 (s, C–H), 1944 (w, C=C=C), 1745 (s, C=O), 1721 (s, C=O), 1500 (s, N–H) cm^{-1}

.^{1}H NMR ($CDCl_3$): δ = 5.21 (d, 1 H, *J* = 5.8 Hz, 3-H), 5.04 (br s, 1 H, NH), 4.75 (d, 1 H, *J* = 5.8 Hz, 2-H), 4.17 (m, 2 H, CH_2), 1.42 [s, 9 H, $OC(CH_3)_3$], 1.25 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.15 [s, 18 H, $CC(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 201.4 (C-4), 171.1 (C-1), 154.8 [$(CH_3)_3COC$], 127.0 (C-5), 89.8 (+, C-3), 79.7 [$OC(CH_3)_3$], 61.3 (–, CH_2), 52.7 (+, C-2), 35.1 [$CC(CH_3)_3$], 32.0 [+, $C(CH_3)_3$], 28.3 [+, $OC(CH_3)_3$], 14.1 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 353 (2, M^+), 297 (90), 224 (100), 168 (60), 151 (45).

Anal. Calcd for $C_{20}H_{35}NO_4$ (353.51): C, 67.96; H, 9.98; N, 3.96. Found: C, 68.00; H, 9.90; N, 4.20.

Ethyl 2-[(*t*-Butoxycarbonyl)amino]-6,6-dimethyl-5-phenylhepta-3,4-dienoate (9c)

CuCN (356 mg, 4.0 mmol) in Et_2O (10 mL), *t*-BuLi (1.5 M in pentane; 5.3 mL, 8.0 mmol), and **8c** (315 mg, 1.0 mmol) in Et_2O (5 mL) furnished **9c** (200 mg, 54%) as a yellow oil.

IR (KBr): 3444 (s), 3368 (s, N–H), 2971 (s), 2933 (s), 2904 (s), 2869 (s, C–H), 1960 (w, C=C=C), 1743 (s, C=O), 1719 (s, C=O), 1492 cm^{-1} (s, N–H).

^{1}H NMR ($CDCl_3$): δ = 7.31–7.20 (m, 5 H, Ph), 5.13 (br s, 1 H, NH), 5.42, 5.40 (2 d, 1 H, *J* = 5.5 Hz, 3-H), 4.88/4.82 (2 × dd, 1 H, *J* = 5.5, 5.8 Hz, 2-H), 4.27–4.07 (m, 2 H, CH_2), 1.43, 1.42 [2 × s, 9 H, $OC(CH_3)_3$], 1.25, 1.19 (2 t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.13 [s, 9 H, $CC(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 200.9, 200.6 (C-4), 170.7, 170.6 (C-1), 154.8, 154.7 [$(CH_3)_3COC$], 136.4 (Ph), 129.1, 127.8, 127.7, 126.9 (4 +, Ph), 120.8, 120.7 (C-5), 89.9, 89.7 (2 +, C-3), 79.8 [$OC(CH_3)_3$], 61.4 (–, CH_2), 52.5 (+, C-2), 34.5 [$CC(CH_3)_3$], 29.6, 29.5 [2 +, $C(CH_3)_3$], 28.3,28.2 [2 +, $OC(CH_3)_3$], 14.0, 13.9 (2 +, CH_2CH_3).

MS (EI): *m*/*z* (%) = 373 (12, M^+), 317 (100), 244 (72), 188 (54), 122 (34).

Anal. Calcd for $C_{22}H_{31}NO_4$ (373.50): C, 70.75; H, 8.37; N, 3.75. Found: C, 70.80; H, 8.40; N, 3.80.

Ethyl 2-[(*t*-Butoxycarbonyl)amino]-6,6-dimethyl-5-(cyclohex-1-en-1-yl)-hepta-3,4-dienoate (9d)

CuCN (1.42 g, 16.0 mmol) in Et_2O (50 mL) , *t*-BuLi (1.5 M in pentane; 21.3 mL, 32.0 mmol), and **8d** (1.30 g, 4.0 mmol) in Et_2O (25 mL) furnished **9d** (950 mg, 63%) as a red oil.

IR (KBr): 3446 (s), 3369 (s, N–H), 2966 (s), 2931 (s), 2868 (s), 2837 (s, C–H), 1953 (w, C=C=C), 1743 (s, C=O), 1721 (s, C=O), 1497 cm^{-1} (s, N–H).

^1H NMR ($CDCl_3$): δ = 5.05 (br s, 1 H, NH), 5.59 (m, 1 H, 2′-H), 5.27 (d, 1 H, *J* = 5.0 Hz, 3-H), 4.79–4.72 (m, 1 H, 2-H), 4.23–4.08 (m, 2 H, CH_2), 2.04–2.02 (m, 4 H, 3′-H, 6′-H), 1.59–1.49 (m, 4 H, 4′-H, 5′-H), 1.40 [s, 9 H, $OC(CH_3)_3$], 1.24, 1.23 (2 × t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.06, 1.05 [2 × s, 9 H, $CC(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 200.7, 200.4 (C-4), 170.9 (C-1), 154.8 [$(CH_3)_3COC$], 132.7, 132.5 (C-1′), 125.9, 125.8 (2 +, C-2′), 122.8, 122.5 (C-5), 89.4, 89.2 (2 +, C-3), 79.7 [$OC(CH_3)_3$], 61.3 (–, CH_2), 52.6, 52.5 (2 +, C-2), 34.2 [$CC(CH_3)_3$], 30.0 [+, $C(CH_3)_3$], 28.3 [+, $OC(CH_3)_3$], 26.8, 25.5 (2 –, C-3′, C-6′), 23.0, 21.8 (2 –, C-4′, C-5′), 14.1 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 377 (5, M^+), 321 (15), 275 (22), 248 (100), 187 (14).

Anal. Calcd for $C_{22}H_{35}NO_4$ (377.53): C, 69.99; H, 9.34; N, 3.71. Found: C, 69.80; H, 9.20; N, 3.80.

Ethyl 2-[(*t*-Butoxycarbonyl)amino]-6,6-dimethyl-5-trimethylsilylhepta-3,4-dienoate (9e)

CuCN (356 mg, 4.0 mmol) in Et_2O (10 mL), *t*-BuLi (1.5 M in pentane; 5.3 mL, 8.0 mmol), and **8e** (311 mg, 1.0 mmol) in Et_2O (5 mL) furnished **9e** (250 mg, 68%) as a yellow oil.

IR (KBr): 3447 (s), 3369 (s, N–H), 2965 (s), 2903 (s), 2871 (s, C–H), 1940 (w, C=C=C), 1744 (s, C=O), 1721 (s, C=O), 1500 cm^{-1} (s, N–H).

^1H NMR ($CDCl_3$): δ = 5.31 (br s, 1 H, NH), 5.13–4.64 (m, 2 H, 2-H, 3-H), 4.19–4.02 (m, 2 H, CH_2), 1.35 [s, 9 H, $OC(CH_3)_3$], 1.18 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.02 [s, 9 H, $CC(CH_3)_3$], 0.08, 0.07 (2 × s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 203.3, 203.1 (C-4), 171.1, 171.0 (C-1), 154.6 [$(CH_3)_3COC$], 115.6 (C-5), 85.0, 84.9 (2 +, C-3), 79.6, 79.5 [$OC(CH_3)_3$], 61.1 (–, CH_2), 52.1, 52.0 (2 +, C-2), 35.1 [$CC(CH_3)_3$], 31.1 [+, $C(CH_3)_3$], 28.2 [+, $OC(CH_3)_3$], 14.0 (+, CH_2CH_3), 0.9 [+, $Si(CH_3)_3$].

MS (EI): *m*/*z* (%) = 369 (5, M^+), 313 (48), 268 (60), 240 (100).

Anal. Calcd for $C_{19}H_{35}NO_4Si$ (369.58): C, 61.75; H, 9.55; N, 3.79. Found: C, 61.80; H, 9.50; N, 3.70.

Ethyl 2-(Acetylamino)-5-*t*-butyl-6,6-dimethylhepta-3,4-dienoate (9f)

CuCN (1.34 g, 15.0 mmol) in Et_2O (50 mL), *t*-BuLi (1.5 M in pentane; 20.0 mL, 30.0 mmol), and **8f** (1.18 g, 5.0 mmol) in Et_2O (25 mL); column chromatography furnished **9f** (621 mg, 42%) as a yellow oil, along with starting material **8f** (533 mg).

IR (KBr): 3292 (s, N–H), 2969 (s), 2957 (s), 2907 (s), 2870 (s, C–H), 1944 (w, C=C=C), 1745 (s, C=O), 1656 (s, C=O), 1536 cm^{-1} (s, N–H).

^1H NMR ($CDCl_3$): δ = 6.35 (br s, 1 H, NH), 5.11 (d, 1 H, *J* = 6.0 Hz, 3-H), 4.90 (dd, 1 H, *J* = 6.0, 6.3 Hz, 2-H), 4.07 (q, 2 H, *J* = 7.0 Hz, CH_2), 1.91 (s, 3 H, $COCH_3$), 1.16 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.06 [s, 18 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 201.3 (C-4), 170.7 ($COCH_3$), 169.1 (C-1), 126.6 (C-5), 89.1 (+, C-3), 61.2 (+, C-2), 61.2 (–, CH_2), 34.8 [$C(CH_3)_3$], 31.8 [+, $C(CH_3)_3$], 22.7 (+, $COCH_3$), 13.9 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 295 (85, M^+), 222 (53), 180 (48), 166 (100).

Anal. Calcd for $C_{17}H_{29}NO_3$ (295.43): C, 69.12; H, 9.89; N, 4.74. Found: C, 69.00; H, 9.90; N, 4.70.

Ethyl 2-Amino-5-*t*-butyl-6,6-dimethylhepta-3,4-dienoate (10)

To a soln (700 mg, 2.0 mmol) of **9b** in dioxane (3 mL) and THF (6 mL) was added HCl (6 N, 8 mL), and the mixture was heated to 80 °C for 6 h and stirred for another 50 h at r.t. After addition of EtOAc (10 mL), the layers were separated, the aqueous phase was washed with EtOAc (3 × 10 mL), the combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo to furnish **10** (435 mg, 87%) as colorless needles; mp 113 °C.

IR (KBr): 3434 (s, N–H), 2957 (s), 2911 (s), 2872 (s, C–H), 1946 (w, C=C=C), 1746 (s, C=O), 1482 cm^{-1} (s, N–H).

^1H NMR ($CDCl_3$): δ = 8.79 (br s, 2 H, NH), 5.44 (d, 1 H, *J* = 7.0 Hz, 3-H), 4.50 (dd, 1 H, *J* = 7.0 Hz, 2-H), 4.26–4.14 (m, 2 H, CH_2), 1.27 (t, 3 H, *J* = 7.3 Hz, CH_2CH_3), 1.16 [s, 18 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 203.8 (C-4), 167.9 (C-1), 126.7 (C-5), 85.6 (+, C-3), 62.4 (–, CH_2), 53.4 (+, C-2), 35.1 [$C(CH_3)_3$], 31.9 [+, $C(CH_3)_3$], 13.9 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 253 (21, M^+), 180 (8), 164 (100).

Anal. Calcd for $C_{15}H_{27}NO_2$ (253.39): C, 71.10; H, 10.74; N, 5.53. Found: C, 71.10; H, 10.70; N, 5.50.

2-(Acetylamino)-5-*t*-butyl-6,6-dimethylhepta-3,4-dienoic Acid (11)

To a soln of **9f** (590 mg, 2.0 mmol) in dioxane (3 mL) and THF (6 mL) was added HCl (6 N, 8 mL), and the mixture was stirred at r.t. for 50 h. After addition of EtOAc (10 mL), the layers were separated, the aqueous phase was washed with EtOAc (3 × 10mL), the combined organic phases were dried with $MgSO_4$, and the solvent was removed in vacuo to furnish **11** (350 mg, 66%) as colorless needles; mp 196 °C/decomp.

IR (KBr): 3600–3300 (m, O–H), 3320 (s, N–H), 2968 (s), 2956 (s), 2922 (s), 2871 (s, C–H), 1942 (w, C=C=C), 1721 (s, C=O), 1610 (s, C=O), 1545 cm^{-1} (s, N–H).

^1H NMR (THF-d_8): δ = 7.25 (s, 1 H, CO_2H), 6.52 (br s, 1 H, NH), 5.21 (d, 1 H, *J* = 6.0 Hz, 3-H), 5.02 (dd, 1 H, *J* = 5.8, 6.0 Hz, 2-H), 1.91 (s, 3 H, $COCH_3$), 1.21 [s, 18 H, $C(CH_3)_3$].

^{13}C NMR (THF-d_8): δ = 203.9 (C-4), 173.4 ($COCH_3$), 170.2 (C-1), 126.9 (C-5), 92.6 (+, C-3), 53.7 (+, C-2), 36.9 [$C(CH_3)_3$], 33.7 [+, $C(CH_3)_3$], 23.7 (+, $COCH_3$).

MS (EI): *m*/*z* (%) = 267 (18, M^+), 210 (7), 193 (15), 152 (100).

Anal. Calcd for $C_{15}H_{25}NO_3$ (267.37): C, 67.38; H, 9.42; N, 5.24. Found: C, 67.30; H, 9.30; N, 5.20.

2-Hydroxy-3,4-dienoates 14; General Procedure[32]

To a soln of *i*-Pr_2NH or hexamethyldisilazane in THF was added at –20 °C *n*-BuLi in hexane. After stirring for 15 min, the mixture was cooled to –80 °C, and a soln of the β-allenic ester **12** in THF was added dropwise. The mixture was stirred for 20 min at –80 °C, and solid Cp_2TiCl_2 was added. The mixture was warmed to –30 °C within 1 h. After cooling to –80 °C, a freshly prepared cold (–20 °C) soln of DMDO in acetone (ca. 0.1 M)[34a] was added rapidly, the cooling bath was removed, and the mixture was warmed to 0 °C. The reaction was then quenched by addition a sat. aq NH_4F soln (2 mL/mmol **12**), and the mixture was stirred for 16 h at r.t. After filtration

through Celite, the solvent was removed in vacuo, and the crude product was purified by column chromatography (SiO_2; cyclohexane–EtOAc, 10:1).

Ethyl 2-Hydroxy-5,6,6-trimethylhepta-3,4-dienoate (14a)
i-Pr_2NH (0.29 g, 2.9 mmol) in THF (15 mL), *n*-BuLi (1.6 M in hexane; 2.0 mL, 3.2 mmol), **12a** (470 mg, 2.4 mmol) [48] in THF (5 mL), Cp_2TiCl_2 (800 mg, 3.2 mmol), and DMDO (35 mL, 3.5 mmol) furnished **12a** (255 mg), and **14a** (157 mg, 68% yield with respect to 46% consumption of **12a**) as a yellow oil (ds 90:10 according to GC and NMR analysis).

IR (neat): 3600–3200 (s, O–H), 2964 (s), 2940 (s), 2911 (s), 2868 (s, C–H), 1962 (w, C=C=C), 1737 cm^{-1} (s, C=O).

^1H NMR (C_6D_6): δ = 5.17 (dq, 1 H, *J* = 6.4, 3.0 Hz, 3-H), 4.56 (d, 1 H, *J* = 6.4 Hz, 2-H), 4.20/4.19 (2 × q, 2 H, *J* = 7.2 Hz, CH_2), 2.88 (s, 1 H, OH), 1.69 (d, 3 H, *J* = 3.0 Hz, 5-CH_3), 1.26 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 1.02 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (C_6D_6): δ = 200.3 (C-4), 173.6 (C-1), 113.0 (C-5), 90.5 (+, C-3), 70.0 (+, C-2), 61.6 (–, CH_2), 33.5 (C-6), 28.9 [+, $C(CH_3)_3$], 14.7 (+, 5-CH_3), 14.1 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 212 (4, M^+), 195 (31), 139 (11), 84 (51), 57 (100).

HRMS (EI) Calcd for $C_{12}H_{20}O_3$ (212.29): 212.1415. Found 212.1414.

Ethyl 2-Hydroxy-2,5,6,6-tetramethylhepta-3,4-dienoate (14b)
i-Pr_2NH (0.56 g, 5.5 mmol) in THF (25 mL), *n*-BuLi (1.6 M in hexane; 3.5 mL, 5.5 mmol), **12b** (1.00 g, 4.8 mmol)[49] in THF (15 mL), Cp_2TiCl_2 (1.37 g, 5.5 mmol), and DMDO (55 mL, 5.5 mmol) furnished **12b** (813 mg) and **14b** (127 mg) (63% yield with respect to 19% consumption of **12b**) as a brown oil (ds 80:20 according to GC and NMR analysis). The analogous reaction with hexamethyldisilazane (342 mg, 2.1 mmol) in THF (35 mL), *n*-BuLi (1.5 M in hexane; 1.7 mL, 2.5 mmol), **12b** (442 mg, 2.1 mmol)[49] in THF (5 mL), Cp_2TiCl_2 (627 mg, 2.5 mmol), and DMDO (35 mL, 3.5 mmol) furnished **12b** (300 mg) and **14b** (115 mg; 75% yield with respect to 32% consumption of **12b**) as a brown oil (ds 80:20 according to GC and NMR analysis).

IR (neat): 3515 (br, O–H), 2966 (s), 2907 (s), 2870 (s, C–H), 1963 (w, C=C=C), 1732 cm^{-1} (s, C=O).

^1H NMR (C_6D_6): δ = 5.37, 5.36* (2 × q, 1 H, *J* = 2.7 Hz, 3-H), 3.91, 3.90* (2 × q, 2 H, *J* = 7.2 Hz, CH_2), 3.51 (s, 1 H, OH), 1.63, 1.60* (2 × d, 3 H, *J* = 2.7 Hz, 5-CH_3), 1.58 (s, 3 H, 2-CH_3), 1.02*, 1.01 [2 × s, 9 H, $C(CH_3)_3$], 0.90 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (C_6D_6): δ = 199.1 (C-4), 175.8*, 175.6 (C-1), 113.4, 113.2* (C-5), 97.3, 97.2* (2 +, C-3), 73.8*, 73.6 (C-2), 61.6, 61.5 (–, CH_2), 33.7*, 33.7 (C-6), 29.1 [+, $C(CH_3)_3$], 25.2, 24.9* (2 +, 2-CH_3), 14.9, 14.9* (+, 5-CH_3), 14.0 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 226 (<1, M^+), 209 (20), 169 (20), 153 (18), 111 (22), 97 (22), 57 (72), 43 (100).

HRMS (FAB) Calcd for $C_{13}H_{22}O_3$ (226.32): 226.1569. Found 226.1593.

Ethyl 2-Hydroxy-5-*t*-butylnona-3,4-dienoate (14c)
i-Pr_2NH (0.56 g, 5.5 mmol) in THF (20 mL), *n*-BuLi (1.6 M in hexane; 3.5 mL, 5.5 mmol)), **12c** (1.27 g, 5.0 mmol)[48] in THF (15 mL), Cp_2TiCl_2 (1.37 g, 5.5 mmol), and DMDO (55 mL, 5.5 mmol) furnished **12c** (573 mg) and **14c** (494 mg, 67% yield with respect to 55% consumption of **12c**) as an orange oil (ds 60: 40 according to GC and NMR analysis). The analogous reaction with hexamethyldisilazane (342 mg, 2.1 mmol) in THF (15 mL), *n*-BuLi (1.5 M in hexane;1.7 mL, 2.5 mmol), **12c** (513 mg, 2.2 mmol)[48] in THF (5 mL), Cp_2TiCl_2 (627 mg, 2.5 mmol), and DMDO (32 mL, 3.2 mmol) furnished **12c** (241 mg) and **14c** (287 mg, 99% yield with respect to 53% consumption of **12c**) as a yellow oil (ds 60:40 according to GC and NMR analysis).

IR (neat): 3502 (br, O–H), 2962 (s), 2932 (s), 2871 (s, C–H), 1958 (w, C=C=C), 1739 (s, C=O), 1733 cm^{-1} (s, C=O).

^1H NMR (C_6D_6): δ = 5.53–5.48 (m, 1 H, 3-H), 4.72 (br s, 1 H, 2-H), 4.05–4.00 (m, 2 H, OCH_2), 3.20, 3.19 (2 × br s, 1 H, OH), 2.06–1.94 (m, 2 H, 6-H), 1.63–1.51 (m, 2 H, 7-H), 1.42 (m, 2 H, 8-H), 1.17, 1.15 [2 × s, 9 H, $C(CH_3)_3$], 1.01 (2 × t, *J* = 7.3 Hz, 6 H, 9-H, OCH_2CH_3).

^{13}C NMR (C_6D_6): δ = 200.4*, 200.3 (C-4), 174.2*, 174.1 (C-1), 119.1, 118.8* (C-5), 94.5, 94.5 (2 +, C-3), 70.5*, 70.4 (2 +, C-2), 61.7 (–, OCH_2), 34.3, 34.2 [$C(CH_3)_3$], 31.0, 31.0 (2 –, C-6), 29.7 [+, $C(CH_3)_3$], 27.5, 27.4 (–, C-7), 23.2 (–, C-8), 14.7, 14.6, 14.4, 14.4 (4 +, C-9, OCH_2CH_3).

MS (EI): *m*/*z* (%) = 254 (<1, M^+), 237 (13), 212 (8), 179 (13), 151 (15), 139 (32), 107 (23), 57 (100).

HRMS (FAB) Calcd for $C_{15}H_{26}O_3$ (254.37): 254.1882. Found 254.1863.

Ethyl 2-Hydroxy-5-butylundeca-3,4-dienoate (14d)
i-Pr_2NH (0.23 g, 2.3 mmol) in THF (25 mL), *n*-BuLi (1.6 M in hexane; 1.5 mL, 2.4 mmol), **12d** (500 mg, 1.9 mmol) in THF (5 mL), Cp_2TiCl_2 (573 mg, 2.3 mmol), and DMDO (40 mL, 4.0 mmol) furnished **12d** (186 mg) and **14d** (290 mg, 87% yield with respect to 63% consumption of **12d**) as a yellow oil (ds 50:50 according to GC and NMR analysis).

IR (neat): 3483 (br, O–H), 2958 (s), 2929 (s), 2858 (s, C–H), 1964 (w, C=C=C), 1738 cm^{-1} (s, C=O).

^1H NMR (C_6D_6): δ = 5.53–5.48 (m, 1 H, 3-H), 4.75 (m, 1 H, 2-H), 4.05–4.00 (m, 2 H, OCH_2), 3.19, 3.17 (2 × br s, 1 H, OH), 2.04–1.99 (m, 4 H, $=CCH_2$), 1.61–1.39 (m, 12 H, 6 × CH_2), 1.03-0.99 (m, 9 H, 3 × CH_3).

^{13}C NMR (C_6D_6): δ = 201.0, 201.0 (C-4), 173.8, 173.8 (C-1), 109.4, 109.3 (C-5), 92.9 (+, C-3), 70.0/70.0 (2 +, C-2), 61.4 (–, OCH_2), 32.9, 32.6, 32.1, 32.1, 30.0, 30.0, 29.4, 27.4, 23.0, 22.8, 22.7 (11 –, CH_2) 14.3, 14.2, 14.1, 14.0 (4 +, CH_3).

MS (ESI): *m*/*z* (%) = 283 (100, M^++1), 265 (99), 242 (87).

Hydroxyallenes 16,17; General Procedure
To a suspension of CuCN in Et_2O was added *n*-Bu_3P or $(EtO)_3P$. The mixture was stirred for 1 h at r.t. and then cooled to –50 °C. The organometallic reagent was added dropwise, and the mixture was stirred for 30 min at –30 °C. After cooling to –80 °C, a soln of the propargylic epoxide **15** in Et_2O was added dropwise, and the mixture was stirred for 1–2 h at –20 °C. Quenching with a sat. NH_4Cl soln (ca. 1 mL/mmol **15**) was followed by filtration through Celite. The filtrate was dried with $MgSO_4$, the solvent was removed in vacuo, and the crude product was purified by column chromatography (SiO_2; cyclohexane–EtOAc, 10:1).

1-(*t*-Butyldimethylsilyloxy)-3,6,6-trimethylhepta-3,4-dien-2-ol (16a)
CuCN (595 mg, 6.7 mmol) in Et_2O (20 mL), *n*-Bu_3P (1.34 g, 6.7 mmol), *t*-BuLi (1.5 M in pentane; 8.9 mL, 13.3 mmol), and *trans*-**15a** (1.25 g, 5.5 mmol)[50] in Et_2O (15 mL) furnished **16a** (1.04 g, 66%) as a pale yellow liquid (ds 65:35 according to GC and NMR analysis).

IR (neat): 3447 (br, O–H), 2958 (s), 2929 (s), 2858 (s, C–H), 1965 cm^{-1} (w, C=C=C).

^1H NMR (C_6D_6): δ = 5.20 (m, 1 H, 5-H), 4.17 (m, 1 H, 2-H), 3.47 (dd, *J* = 10.0, 4.0 Hz, 1 H, 1-H), 3.66 (m, 1 H 1-H), 2.59*, 2.56 (2

s, 1 H, OH), 1.80 (s, 3 H, 3-CH_3), 1.04, 1.03* [2 × s, 9 H, 5-$C(CH_3)_3$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 0.04, 0.04 [2 × s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (C_6D_6): δ = 198.4, 198.2* (C-4), 104.9, 104.8* (2 +, C-5), 102.5, 102.3* (C-3), 73.0*, 72.9 (2 +, C-2), 66.9, 66.8* (2 –, C-1), 32.2, 32.2* (C-6), 30.4, 30.3 [2 +, 5-$C(CH_3)_3$], 26.1 [+, $SiC(CH_3)_3$], 18.5, 18.5* [$SiC(CH_3)_3$], 16.0*, 15.8 (2 +, 3-CH_3), –5.5*, –5.5 [2 +, $Si(CH_3)_2$].

MS (EI): *m*/*z* (%) = 283 (<1, M^+–1), 171 (15), 135 (60), 119 (30), 107 (60), 91 (50), 75 (100).

1-Methoxy-3,5,6,6-tetramethylhepta-3,4-dien-2-ol (16b)
CuCN (595 mg, 6.7 mmol) in Et_2O (20 mL), $(EtO_3)P$ (1.10 g, 6.7 mmol), *t*-BuLi (1.3 M in pentane; 10.1 mL, 13.3 mmol), and *trans*-**15b** (777 mg, 5.5 mmol)[51] in Et_2O (15 mL) furnished **16b** (723 mg, 66%) as a pale yellow liquid (ds 80:20 according to GC and NMR analysis).

IR (neat): 3447 (br, O–H), 2963 (s, C–H), 1964 cm^{-1} (w, C=C=C).

^{1}H NMR (C_6D_6): δ = 4.37 (m, 1 H, 2-H), 3.51–3.43 (m, 2 H 1-H), 3.19 (s, 3 H, OCH_3), 2.73 (br s, 1 H, OH), 1.89*, 1.88 (2 × s, 3 H, 3-CH_3), 1.75, 1.74 (2 × s, 3 H, 5-CH_3), 1.15, 1.14 [2 × s, 9 H, 5-$C(CH_3)_3$].

^{13}C NMR (C_6D_6): δ = 197.5*, 197.3 (C-4), 110.4, 110.0* (C-3), 99.9, 99.6* (C-5), 76.3 (–, C-1), 71.7, 71.6 (2 +, C-2), 58.6 (+, OCH_3), 34.0, 33.9 (C-6), 29.3 [+, $C(CH_3)_3$], 16.1, 16.0*, 15.2, 15.1* (4 +, 3-CH_3, 5-CH_3).

MS (FAB): *m*/*z* (%) = 198 (10, M^+), 181 (100).

HRMS (FAB) Calcd for $C_{12}H_{22}O_2$ (198.31): 198.1620. Found 198.1641.

1-(*t*-Butyldimethylsilyloxy)-3-methylundeca-3,4-dien-2-ol (16c)
CuCN (595 mg, 6.7 mmol) in Et_2O (20 mL), *n*-Bu_3P (1.34 g, 6.7 mmol), *n*-HexLi (2.5 M in hexane; 5.3 mL, 13.3 mmol), *cis*-**15a** (1.25 g, 5.5 mmol)[50] in Et_2O (15 mL) furnished **16c** (1.32 g, 77%) as a pale yellow liquid (ds 75:25 according to GC and NMR analysis), containing 15% of the corresponding reduction product **17a**.

IR (neat): 3374 (br, O–H), 2957 (s), 2928 (s), 2857 (s, C–H), 1962 cm^{-1} (w, C=C=C).

^{1}H NMR (C_6D_6): δ = 5.18 (m, 1 H, 5-H), 4.20 (m, 1 H, 2-H), 3.74 (dd, 1 H, *J* = 10.0, 4.3 Hz, 1-H), 3.67 (dd, 1 H, *J* = 10.0, 6.8 Hz, 1-H), 2.61 (s, 1 H, OH), 1.96 (m, 2 H, 6-H), 1.81, 1.81 (2 × s, 3 H, 3-CH_3), 1.44–1.25 (m, 8 H, 7-H, 8-H, 9-H, 10-H), 0.94–0.89 [m, 12 H, 11-H, $SiC(CH_3)_3$], 0.05, 0.04 [2 × s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (C_6D_6): δ = 201.3, 201.2* (C-4), 100.6 (C-3), 92.9, 92.9 (2 +, C-5), 73.1, 72.9* (2 +, C-2), 66.7*, 66.7 (2 –, C-1), 32.3*, 32.0 (2 –, C-6), 30.2, 30.1, 29.8, 29.6, 29.5, 29.2, 23.1, 23.0 (8 –, C-7, C-8, C-9, C-10), 26.1 [+, $SiC(CH_3)_3$], 18.5 [$SiC(CH_3)_3$], 15.8 (+, 3-CH_3), 14.4*, 14.3 (2 +, C-11), –5.3, –5.2 [2 +, $Si(CH_3)_2$].

MS (EI): *m*/*z* (%) = 312 (<1, M^+), 297 (<1), 255 (10), 171 (35), 107 (30), 93 (40), 75 (100).

1-(*t*-Butyldimethylsilyloxy)-3-methylhexa-3,4-dien-2-ol (16d)
CuCN (238 mg, 2.7 mmol) in Et_2O (30 mL), *n*-Bu_3P (537 mg, 2.7 mmol), MeLi (1.6 M in Et_2O; 3.3 mL, 5.3 mmol), and *cis*-**15a** (500 mg, 2.2 mmol)[50] in Et_2O (5 mL) furnished **16d** (414 mg, 77%) as a yellow liquid (ds 85:15 according to GC and NMR analysis). Alternatively, CuCN (238 mg, 2.7 mmol) in Et_2O (20 mL), *n*-Bu_3P (537 mg, 2.7 mmol), MeMgBr (3.0 M in Et_2O; 1.8 mL, 5.3 mmol), and *cis*-**15a** (500 mg, 2.2 mmol)[50] in Et_2O (5 mL) furnished **16d** (373 mg, 70%) as a pale yellow liquid (ds 94:6 according to GC and NMR analysis).

IR (neat): 3436 (br, O–H), 2930 (s), 2885 (s), 2858 (s, C–H), 1968 cm^{-1} (w, C=C=C).

^{1}H NMR (C_6D_6): δ = 5.17 (m, 1 H, 5-H), 4.24 (m, 1 H, 2-H), 3.80–3.69 (m, 2 H 1-H), 2.50 (s, 1 H, OH), 1.86, 1.85 (2 × s, 3 H, 3-CH_3), 1.64, 1.62 (2 × s, 3 H, 6-H), 1.02, 1.01 [2 × s, 9 H, $C(CH_3)_3$], 0.12 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (C_6D_6): δ = 202.0, 201.9 (C-4), 100.0 (C-3), 87.5, 87.4 (2 +, C-5), 73.0, 72.8 (2 +, C-2), 66.5, 66.4 (2 –, C-1), 26.0 [+, $C(CH_3)_3$], 18.5 [$C(CH_3)_3$], 15.6, 15.5 (2 +, C-6, 3-CH_3), –5.3 [+, $Si(CH_3)_2$].

MS (FAB): *m*/*z* (%) = 245 (5, M^+–1), 73 (100).

1-(*t*-Butyldimethylsilyloxy)-3-methylpenta-3,4-dien-2-ol (17a)
From CuCN (297 mg, 3.3 mmol) in Et_2O (25 mL), MeLi (1.6 M in Et_2O; 4.1 mL, 6.6 mmol), and *trans*-**15a** (500 mg, 2.2 mmol)[50] in Et_2O (5 mL). Deviating from the general procedure, no phosphine or phosphite was added, and the mixture was stirred for 2 h at –80 °C before quenching with NH_4Cl soln at this temperature. This furnished **17a** (437 mg, 87%) as a yellow liquid, containing 20% of the corresponding substitution product **16d**.

IR (neat): 3442 (br, O–H), 2955 (s), 2929 (s), 2858 (s, C–H), 1960 cm^{-1} (w, C=C=C).

^{1}H NMR (C_6D_6): δ = 4.64–4.62 (m, 2 H, 5-H), 4.15 (m, 1 H, 2-H), 3.67 (dd, 1 H, *J* = 10.0, 3.2 Hz, 1-H), 3.61 (dd, *J* = 10.0, 7.0 Hz, 1 H, 1-H), 2.54 (s, 1 H, OH), 1.73 (t, 3 H, *J* = 3.2 Hz, 3-CH_3), 0.91 [s, 9 H, $C(CH_3)_3$], 0.01 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (C_6D_6): δ = 206.0 (C-4), 99.6 (C-3), 76.0 (–, C-5), 72.5 (+, C-2), 66.0 (–, C-1), 26.0 [+, $C(CH_3)_3$], 18.5 [$C(CH_3)_3$], 15.0 (+, 3-CH_3), –5.3 [+, $Si(CH_3)_2$].

MS (FAB): *m*/*z* (%) = 229 (3, M^+ + 1), 73 (100).

1-Methoxy-3,6-dimethylhexa-3,4-dien-2-ol (16e)
From CuCN (383 mg, 4.3 mmol) in Et_2O (30 mL), MeLi (1.6 M in Et_2O; 5.4 mL, 8.6 mmol), and *trans*-**15b** (500 mg, 3.8 mmol) in Et_2O (5 mL). Deviating from the general procedure, no phosphine or phosphite was added, and the mixture was stirred for 2 h at –80 °C before quenching with NH_4Cl soln at this temperature. This furnished **16e** (469 mg, 88%) as a pale yellow liquid, containing 10% of the corresponding reduction product **17b**.

IR (neat): 3439 (br, O–H), 2986(s), 2981 (s), 2906 (s, C–H), 1970 cm^{-1} (w, C=C=C).

^{1}H NMR (C_6D_6): δ = 4.38 (m, 1 H, 2-H), 3.50–3.43 (m, 2 H 1-H), 3.20 (s, 3 H, OCH_3), 2.82 (br s, 1 H, OH), 1.88 (s, 3 H, 3-CH_3), 1.70, 1.70 (2 × s, 6 H, 5-CH_3).

^{13}C NMR (C_6D_6): δ = 198.8 (C-4), 98.3, 96.7 (C-3, C-5), 76.3 (–, C-1), 71.7 (+, C-2), 58.6 (+, OCH_3), 20.8, 20.7 (2 +, 5-CH_3), 15.9 (+, 3-CH_3).

MS (FAB): *m*/*z* (%) = 156 (13, M^+), 73 (100).

HRMS (FAB) Calcd for $C_9H_{16}O_2$ (156.22): 156.1150. Found 156.1156.

Cyclization of α-Hydroxyallenes 14,16,17 to 2,5-Dihydrofurans 18: General Procedure

Method A
Into a soln of the hydroxyallene **14** in anhyd $CHCl_3$ or $CDCl_3$, HCl gas was introduced for 2 min. The reaction was monitored by TLC; after complete consumption (usually 1 h), the solvent was removed under reduced pressure, giving spectroscopically pure dihydrofuran **18**. This material can be further purified by flash chromatography (SiO_2; cyclohexane–EtOAc, 10:1). **Attention**: Long exposure to silica gel may cause considerable decomposition of the dihydrofuran.

Method B
To a soln of the hydroxyallene **14** in anhyd CH_2Cl_2 was added Amberlyst 15 resin, and the mixture was heated to reflux for 1–2 h. Af-

ter cooling to r.t. and filtration, the solvent was removed in vacuo, giving spectroscopically pure dihydrofuran **18**. This material can be further purified by flash chromatography (SiO_2; cyclohexane–EtOAc, 10:1). **Attention**: Longer exposure to silica gel may cause considerable decomposition of the dihydrofuran.

Method C

To a soln of the hydroxyallene under argon in anhyd CH_2Cl_2 was added $AuCl_3$ (5–10 mol%) (99%, Aldrich), and the mixture was stirred at r.t. After completion (TLC control), the solvent was evaporated in vacuo. Flash column chromatography (SiO_2; cyclohexane–EtOAc, 10:1) afforded the 2,5-dihydrofuran **18**. **Attention**: Long exposure to silica gel may cause considerable decomposition of the dihydrofuran. Gold(III)-chloride is hygroscopic; the reaction proceeds sluggishly with material that has been exposed to moisture.

Ethyl 5-*t*-Butyl-5-methyl-2,5-dihydrofurancarboxylate (18a)

Method A: Compound **14a** (124 mg, 0.58 mmol) in $CDCl_3$ (2 mL) furnished **18a** (112 mg, 90%) as a yellow liquid (ds 90:10 according to GC and NMR analysis).

Method B: Compound **14a** (90 mg, 0.42 mmol) in CH_2Cl_2 (15 mL), and Amberlyst 15 (200 mg) furnished **18a** (90 mg, quant.) as a yellow liquid (ds 90:10 according to GC and NMR analysis).

Method C: Compound **14a** (134 mg, 0.63 mmol) in CH_2Cl_2 (5 mL), and $AuCl_3$ (9.6 mg, 0.03 mmol) furnished **18a** (98 mg, 74%) as a yellow liquid (ds 90:10 according to GC and NMR analysis).

IR (neat): 3084 (w, =C–H), 2972 (s), 2909 (s), 2873 (s, C–H), 1758 (s), 1732 cm^{-1} (s, C=O).

^1H NMR (C_6D_6): δ = 5.56 (m, 2 H, 3-H, 4-H), 5.13 (m, 1 H, 2-H), 3.91 (m, 2 H, CH_2), 1.41 (s, 3 H, 5-CH_3), 0.91 [m, 12 H, $C(CH_3)_3$, CH_2CH_3].

NOESY: Crosspeak between δ = 5.13 (5-H) and 1.41 (5-CH_3).

^{13}C NMR (C_6D_6): δ = 171.0*, 170.1 (CO_2CH_2), 135.2 (+, C-4), 124.4*, 124.2 (+, C-3), 97.7*, 97.1 (C-5), 85.3*, 83.5 (+, C-2), 60.6*, 60.5 (–, CH_2), 38.0*, 37.1 [$C(CH_3)_3$], 26.2, 25.7* [+, $C(CH_3)_3$], 22.6*, 21.5 (+, 5-CH_3), 14.1 (+, CH_2CH_3).

MS (EI): *m*/*z* (%) = 212 (<1, M^+), 171 (7), 155 (10), 125 (16), 98 (100).

Ethyl 5-*t*-Butyl-2,5-dimethyl-2,5-dihydrofurancarboxylate (18b)

Method A: Compound **14b** (50 mg, 0.22 mmol) in $CDCl_3$ (1 mL) furnished **18b** (46 mg, 92%) as brown liquid (ds 80:20 according to GC and NMR analysis).

IR (neat): 3079 (w, =C–H), 2978 (s), 2872 (s, C–H), 1750 (s), 1730 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$): δ = 5.75 (d, 1 H, *J* = 6.0 Hz, 3-H), 5.61 (d, 1 H, *J* = 6.0 Hz, 4-H), 4.13–3.96 (m, 2 H, CH_2), 1.40 (s, 3 H, 2-CH_3), 1.19 (s, 3 H, 5-CH_3), 1.14 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 0.82 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 174.1 (CO_2CH_2), 134.2, 133.4* (2 +, C-4), 128.7, 128.4* (2 +, C-3), 96.7*, 96.1 (C-5), 89.8, 89.2* (C-2), 61.0*, 60.8 (2 –, OCH_2), 37.2, 36.7* [$C(CH_3)_3$], 26.1 [+,$C(CH_3)_3$], 24.0*, 23.5 (2 +, 2-CH_3), 21.9 (+, 5-CH_3), 14.1, 14.0* (2 +, CH_2CH_3).

MS (EI): *m*/*z* (%) = 180 (<1, $M^+ - C_2H_6O$), 169 (2, $M^+ - C_4H_9$), 127 (20), 109 (20), 97 (100).

Ethyl 5-Butyl-5-*t*-butyl-2,5-dihydrofurancarboxylate (18c)

Method A:Compound **14c** (100 mg, 0.39 mmol) in $CDCl_3$ (1 mL) furnished **18c** (80 mg, 80%) as an orange liquid (ds 60:40 according to GC and NMR analysis).

Method C: Compound **14c** (100 mg, 0.39 mmol) in CH_2Cl_2 (5 mL), and $AuCl_3$ (10 mg, 0.03 mmol) furnished **18c** (100 mg, quant.) as an orange liquid (ds 60:40 according to GC and NMR analysis).

IR (neat): 3084 (w, =C–H), 2959 (s), 2872 (s, C–H), 1761 (s), 1732 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$): δ = 5.86 (m, 1 H, 3-H), 5.73 (m, 1 H, 4-H), 5.15 (m, 1 H, 2-H), 4.17 (m, 2 H, OCH_2), 1.84–1.52 (m, 2 H, 5-CH_2), 1.30–1.20 (m, 7 H, CH_2CH_2, OCH_2CH_3), 0.90 [s, 9 H, $C(CH_3)_3$], 0.83 (t, 3 H, *J* = 7.2 Hz, $CH_2CH_2CH_3$).

^{13}C NMR ($CDCl_3$): δ = 170.6*, 170.3 (CO_2CH_2), 132.9*, 132.5 (+, C-4), 125.0*, 124.6 (+, C-3), 100.6*, 100.3 (C-5), 85.1*, 85.0 (+, C-2), 60.8*, 60.7 (–, CH_2), 39.3*, 37.3 [$C(CH_3)_3$], 33.5, 32.7* (–, 5-CH_2), 26.9, 26.2 (–, 5-CH_2CH_2), 26.4, 26.1* [+, $C(CH_3)_3$], 22.6*, 21.5 (+, 5-CH_3), 14.1, 14.1 (2 +, $CH_2CH_2CH_3$, OCH_2CH_3).

MS (EI): *m*/*z* (%) = 255 (10, $M^+ - 1$), 197 (70), 181 (15), 125 (20), 81 (45), 57 (100).

Ethyl 5-Butyl-5-hexyl-2,5-dihydrofurancarboxylate (18d)

Method A: Compound **14d** (50 mg, 0.18 mmol) in $CDCl_3$ (1 mL) furnished **18d** (45 mg, 90%) as a yellow liquid (ds 50:50 according to GC and NMR analysis).

IR (neat): 3080 (w, =C–H), 2976 (s), 2872 (s, C–H), 1758 (s), 1733 cm^{-1} (s, C=O).

^1H NMR (C_6D_6): δ = 5.66 (d, 1 H, *J* = 5.9 Hz, 4-H), 5.44 (dd, 1 H, *J* = 5.9, 2.7 Hz, 3-H), 5.21 (m, 1 H, 2-H), 3.93 (m, 2 H, OCH_2), 1.85–0.85 (m, 25 H, CH_2, CH_3).

^{13}C NMR (C_6D_6): δ = 170.7 (CO_2CH_2), 135.5, 135.5 (2 +, C-3), 124.8 (+, C-4), 95.2 (C-5), 84.8 (+, C-2), 60.65 (–, OCH_2), 40.4, 40.1, 39.5, 39.3 (4 –, C-1′, C-1′′), 32.3, 32.3, 30.3, 30.2, 26.7, 26.5, 24.5, 24.3, 23.6, 23.5, 23.0 (11 –, CH_2), 14.4, 14.3, 14.2 (3 +, CH_3).

MS (EI): *m*/*z* (%) = 282 (<1, M^+), 225 (75), 209 (100), 197 (65), 153 (40), 125 (35), 81 (55).

5-*t*-Butyl-2-(*t*-butyldimethylsilyloxymethyl)-3-methyl-2,5-dihydrofuran (18e)

Method C: Compound **16a** (250 mg, 0.88 mmol) in CH_2Cl_2 (5 mL) and $AuCl_3$ (19 mg, 0.06 mmol) furnished **18e** (238 mg, 95%) as a yellow liquid (ds 65:35 according to GC and NMR analysis).

IR (neat): 3069 (w, = C–H), 2955 (s), 2929 (s), 2858 cm^{-1} (s, C–H).

^1H NMR (C_6D_6): δ = 5.29*, 5.24 (dd, 1 H, *J* = 3.0, 1.5 Hz, 4-H), 4.64, 4.59* (m, 1 H, 2-H), 4.49*, 4.42 (m, 1 H, 5-H), 3.74–3.60 (m, 2 H, CH_2), 1.62, 1.61* (d, 3 H, *J* = 0.5 Hz, 3-CH_3), 0.98–0.94 [m, 18 H, 5-$C(CH_3)_3$, $SiC(CH_3)_3$], 0.08–0.05 [m, 6 H, $Si(CH_3)_2$].

^{13}C NMR (C_6D_6): δ = 139.0, 138.4* (C-3), 123.4, 123.3 (+, C-4), 94.0, 93.5 (2 +, C-5), 88.9*, 88.1 (+, C-2), 66.4, 65.5* (–, CH_2), 35.9*, 34.5 [5-$C(CH_3)_3$], 26.1, 25.3 [2 +, 5-$C(CH_3)_3$, $SiC(CH_3)_3$], 18.5, 18.4 [$SiC(CH_3)_3$], 13.0, 12.8* (+, 3-CH_3), –5.2, –5.3 [+, $Si(CH_3)_2$].

MS (EI): *m*/*z* (%) = 283 (15, $M^+ - 1$), 269 (25, $M^+ - CH_3$), 227 (35), 157 (10), 135 (45), 111 (25), 89 (100).

5-*t*-Butyl-3,5-dimethyl-2-methoxymethyl-2,5-dihydrofuran (18f)

Method C: Compound **16b** (269 mg, 1.36 mmol) in CH_2Cl_2 (5 mL), and $AuCl_3$ (20.6 mg, 0.07 mmol) furnished **18f** (242 mg, 90%) as yellow liquid (ds 80:20 according to GC and NMR analysis).

IR (neat): 3075 cm^{-1} (w, =C–H), 2966 (s), 2931 (s), 2857 (s, C–H).

^1H NMR ($CDCl_3$): δ = 5.46 (m, 1 H, 4-H), 4.69, 4.61* (m, 1 H, 2-H), 3.52–3.37 (m, 2 H, CH_2), 3.38, 3.37* (s, 3 H, OCH_3), 1.70*, 1.68 (s, 3 H, 3-CH_3), 1.23*, 1.18 (s, 3 H, 5-CH_3), 0.95, 0.89 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 134.6 (C-3), 128.7, 128.4* (+, C-4), 94.4*, 94.0 (C-5), 87.5*, 85.0 (+, C-2), 75.1*, 74.9 (–, CH_2), 59.3*, 59.2 (+, OCH_3), 38.5 [$C(CH_3)_3$], 26.1, 25.6* [+, $C(CH_3)_3$], 22.9*, 21.3 (+, 5-CH_3), 12.4 (+, 3-CH_3).

MS (EI): *m*/*z* (%) = 183 (5, M^+-CH_3), 141 (100), 154 (7), 109 (30).

2-(*t*-Butyldimethylsilyloxymethyl)-5-hexyl-3-methyl-2,5-dihydrofuran (18g)

Method C: Compound **16c** (257 mg, 0.82 mmol) in CH_2Cl_2 (5 mL), and $AuCl_3$ (12.5 mg, 0.04 mmol) furnished **18g** (166 mg, 65%) as a yellow liquid (ds 75:25 according to GC and NMR analysis).

IR (neat): 3070 (w, =C–H), 2956 (s), 2926 (s), 2856 cm^{-1} (s, C–H).

^{1}H NMR ($CDCl_3$): δ = 5.43 (m, 1 H, 4-H), 4.74, 4.67* (m, 1 H, 5-H), 4.55 (m, 1 H, 2-H), 3.68-3.65 (m, 2 H, OCH_2), 1.72 (s, 3 H, 3-CH_3), 1.26 [m, 10 H, $(CH_2)_5$], 0.99–0.94 [m, 12 H, CH_2CH_3, $C(CH_3)_3$], 0.06–0.03 [m, 6 H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$): δ = 136.7, 136.6* (C-3), 125.5, 125.4* (+, C-4), 88.1*, 87.9 (+, C-2), 85.5, 85.4* (+, C-5), 65.7*, 65.1 (–, CH_2), 37.2*, 36.6 (–, 5-CH_2), 31.9*, 31.9, 29.7*, 29.7, 29.4, 29.4*, 22.7*, 22.6 [4–, $(CH_2)_4$], 25.8 [+, $C(CH_3)_3$], 18.3 [$C(CH_3)_3$], 14.1 [+, CH_2CH_3], 12.8 (+, 3-CH_3), –5.4, –-5.5 [+, $Si(CH_3)_2$].

2-(*t*-Butyldimethylsilyloxymethyl)-3,5-dimethyl-2,5-dihydrofuran (18h)

Method C: Compound **16a** (362 mg, 1.50 mmol) in CH_2Cl_2 (10 mL), and $AuCl_3$ (45 mg, 0.15 mmol) furnished **18h** (279 mg, 77%) as a yellow liquid (ds 94:6 according to GC and NMR analysis).

IR (neat): 3065 (w, =C–H), 2956 (s), 2929 (s), 2885 (s), 2858 cm^{-1} (s, C–H).

^{1}H NMR (C_6D_6): δ = 5.20, 5.16 (m, 1 H, 4-H), 4.91, 4.83* (m, 1 H, 5-H), 4.64, 4.59* (m, 1 H, 2-H), 3.69–3.59 (m, 2 H, CH_2), 1.56 (s, 3 H, 3-CH_3), 1.23 (d, 3 H, *J* = 6.3 Hz, 5-CH_3), 0.97–0.93 [m, 9 H, $C(CH_3)_3$], 0.06–0.03 [m, 6 H, $Si(CH_3)_2$].

NOESY: Crosspeak between δ = 4.83 (5-H, major diastereomer) and 4.59 (2-H, major diastereomer).

^{13}C NMR (C_6D_6): δ = 136.6 (C-3), 127.4, 127.2* (+, C-4), 88.6*, 88.2 (+, C-2), 81.5, 81.3* (+, C-5), 65.9*, 65.3 (–, CH_2), 26.1 [+, $C(CH_3)_3$], 23.0*, 22.5 (+, 5-CH_3), 18.5 [$C(CH_3)_3$], 12.7 (+, 3-CH_3), –5.2, –5.3 [+, $Si(CH_3)_2$].

MS (EI): *m*/*z* (%) = 241 (20, $M^+ - 1$), 227 (35, $M^+ - CH_3$), 185 (100), 155 (12), 141 (27), 109 (48), 97 (100).

2-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-2,5-dihydrofuran (18i)

Method C: Compound **17a** (230 mg, 1.01 mmol) in CH_2Cl_2 (5 mL), and $AuCl_3$ (12 mg, 0.04 mmol) furnished **18i** (198 mg, 86%) as a pale yellow liquid.

IR (neat): 3063 cm (w, =C–H), 2955 (s), 2929 (s), 2857 $^{-1}$ (s, C–H).

^{1}H NMR (C_6D_6): δ = 5.20 (m, 1 H, 4-H), 4.57–4.47 (m, 3 H, 2-H, 5-H), 3.69 (dd, 1 H, *J* = 11.0, 3.8 Hz, 2-CH_2), 3.62 (dd, 1 H, *J* = 11.0, 3.5 Hz, 2-CH_2), 1.55 (s, 3 H, 3-CH_3), 0.96 [s, 9 H, $C(CH_3)_3$], 0.07 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (C_6D_6): δ = 136.6 (C-3), 122.1 (+, C-4), 88.6 (+, C-2), 74.9 (–, C-5), 65.2 (–, 2-CH_2), 26.0 [+, $C(CH_3)_3$], 18.5 [$C(CH_3)_3$], 12.7 (+, 3-CH_3), –5.3 [+, $Si(CH_3)_2$].

5,6-Epoxy-5-methylbut-3-yn-2-ol (26)

To a soln of **25** (2.50 g, 22.7 mmol)[44] in CH_2Cl_2 (120 mL) was added successively at 0 °C Na_2HPO_4 (6.06 g, 34.0 mmol) and (8.39 g, 34.0 mmol) of *m*CPBA (70%). The mixture was stirred and warmed up gradually to r.t. within 16 h; after hydrolysis with a sat. Na_2CO_3 soln (100 mL), the layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 30 mL). The combined layers were washed with 1% NaOH (50 ML), a sat. Na_2CO_3 soln (3 × 25 mL), and brine (25 mL). After drying with $MgSO_4$, the solvent was removed under reduced pressure, to give crude **26** (1.65 g, 58%; ds 60:40 according to NMR analysis) which was used without purification in the next step.

IR (neat): 3403 (br, O–H), 2984 (s), 2934 cm^{-1} (s, C–H).

^{1}H NMR (C_6D_6): δ = 4.47 (q, 1 H, *J* = 6.6 Hz, 2-H), 3.00 (br s, 1 H, OH), 2.95 (d, 1 H, *J* = 5.5 Hz, 6-H), 2.71 (d, 1 H, *J* = 5.5 Hz, 6-H), 1.48 (s, 3 H, 5-CH_3), 1.37 (d, 3 H, *J* = 6.6 Hz, 1-H).

^{13}C NMR (C_6D_6): δ = 84.1, 83.3 (C-3, C-4), 57.8 (+, C-2), 55.3 (–, C-6), 47.2 (C-5), 23.9 (+, C-1), 22.7 (+, 5-CH_3).

2,4-Dimethylhexa-2,3-dien-1,5-diol (27)[26f]

CuCN (887mg, 9.9 mmol) in Et_2O (25 mL), MeMgBr (3.0 M in Et_2O; 6.6 mL, 19.8 mmol), and **26** (625 mg, 5.0 mmol) in Et_2O (15 mL) according to the general procedure for the preparation hydroxyallenes **16**,**17** (no phosphine added) furnished **27** (300 mg, 43%) as a yellow oil (ds 60:40 according to NMR analysis).

^{1}H NMR (C_6D_6): δ = 4.54–4.47 (m, 2 H, OH), 4.34, 4.14 (2 × q, *J* = 6.5 Hz, 1 H, 5-H), 4.08–4.01 (m, 2 H, 1-H), 1.75, 1.74 (2 × d, 3 H, 2-CH_3, 4-CH_3), 1.66 (s, 3 H, 2-CH_3, 4-CH_3), 1.35, 1.33 (2 × d, 3 H, *J* = 6.5 Hz, 6-H).

^{13}C NMR (C_6D_6): δ = 196.8*, 196.3 (C-3), 106.9, 106.1*, 103.1, 101.5* (C-2, C-4), 69.5*, 69.1 (2 +, C-5), 64.2, 64.0 (2 –, C-1), 22.3, 21.7* (2 +, C-6), 16.7, 16.1*, 14.2 (3 +, 2-CH_3, 4-CH_3).

2-(*t*-Butyldimethylsilyloxymethyl)-2,4,5-trimethyl-2,5-dihydrofuran (22)[26f]

A soln of **27** (300 mg, 2.1 mmol) in CH_2Cl_2 (30 mL) was treated successively with a small amount DMAP, Et_3N (0.35 mL, 2.5 mmol), and TBSCl (350 mg, 2.3 mmol). After stirring for 4 h at r.t., a sat. $NaHCO_3$ soln (10 mL) was added, the layers were separated, the aqueous layer was washed CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed brine (2 × 10 mL) and dried with $MgSO_4$. Removal of the solvent in vacuo followed by column chromatography (SiO_2; cyclohexane–EtOAc, 5:1) furnished **23** (307 mg, 57%) as a colorless liquid. This was immediately dissolved in CH_2Cl_2 (5 mL), and treated with $AuCl_3$ (17.6 mg, 0.06 mmol) according to the general procedure for the cyclization of α-hydroxyallenes **14**,**16**,**17** to 2,5-dihydrofurans **18** (Method C) to give **22** (245 mg, 80%) as a pale yellow liquid (ds 60:40 according to GC and NMR analysis).

^{1}H NMR (C_6D_6): δ = 5.32, 5.27 (2 × s, 1 H, 4-H), 4.70 (q, *J* = 6.2 Hz, 5-H), 3.58 (s, CH_2), 1.42, 1.40 (2 × s, 3-CH_3), 1.38, 1.37 (2 × s, 2-CH_3), 1.20, 1.19 (2 × d, *J* = 6.2 Hz,, 5-CH_3), 0.98 [s, 9 H, $C(CH_3)_3$], 0.07, 0.06 [2 × s, $Si(CH_3)_2$].

^{13}C NMR (C_6D_6): δ = 140.3, 139.8 (C-3), 126.8, 126.7 (2 +, C-4), 89.3, 89.0 (C-2), 83.7, 83.2 (2 +, C-5), 71.5, 70.4 (2 –, CH_2), 26.1, 26.0 [2 +, $C(CH_3)_3$], 24.9, 23.7 (2 +, 5-CH_3), 21.9, 21.6 (2 +, 2-CH_3), 18.6, 18.5 [$C(CH_3)_3$], 12.2, 12.1 (2 +, 3-CH_3), –5.2, –5.3 [+, $Si(CH_3)_2$].

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