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Cyclization of 1,5-Dienes: An Efficient Synthesis of β-Georgywood

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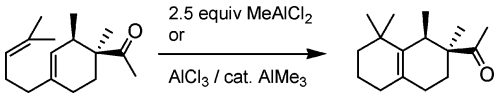
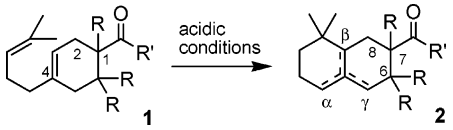


In the acid-promoted 1,5-diene cyclization of pseudo- to β-Georgywood, the cyclization product is obtained with high selectivity in spite of an unfavorable substituent at the C(2)-position of the diene precursor. Preisomerization of the cyclohexene double bond, which occurs in the presence of Brønsted acids, is suppressed with >1 equiv of MX_n-type Lewis acids, whereas $RAlX_2$-type Lewis acids such as >2 equiv of $MeAlCl_2$ have the additional benefit of steering the double bond of the cyclized product into the desired β-position. Mechanistic studies revealed a crucial participation or nonparticipation of the carbonyl group in the cyclization reaction, depending on the acid family employed, and allowed finally the development of a cyclization reaction catalyzed by $MeAlCl_2$ that can be generated in situ from precatalyst $AlMe_3$.[1]

More than 50 years ago, Eschenmoser, Stork, and others published their fundamental investigations on the mechanism of cationic 1,5-diene cyclization reactions.[2] Fragrance chemists first used 1,5-diene cyclization reactions at the end of the 19th century (e.g., for the synthesis of Ionone or Geranitrile)[3] and their use continues up to the present time.[4] Also in the fifties, Ohloff communicated the acid-promoted 1,5-diene cyclization of 1-[4-(isohexenylcyclohex-3-enyl]alkan-1-ones **1**. The cyclization products **2** had interesting woody-ambery odor properties (Scheme 1), depending on the substitution pattern at C(6) and C(7).[5]

SCHEME 1[a]



[a] Reagents and conditions: R = H or alkyl. R′ = H, alkyl, or OR. The α,β,γ denotation of the double bond isomers of **2** goes back to ref 5.

Some of these products (**2**) or their derivatives were commercialized, e.g., Lactoscatone **3**, Cyclemone A (or Aldehyde 111) **2a**, and Iso E Super **2b** (Figure 1). The latter compound (**2b**) ultimately became one of the most important fragrance ingredients of the woody-ambery family.[6]

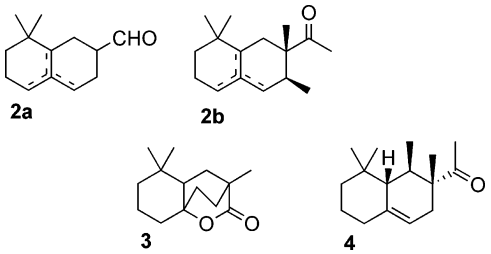


FIGURE 1. Commercialized compounds prepared via the cyclization of Scheme 1. Compound **2b** contains ca. 3% of impurity **4**.

Inspired by the finding that the olfactorily most powerful vector of Iso E Super is not an isomer of **2b**, but impurity **4**,[7] Fráter et al. examined 1,5-diene **5** as a cyclization precursor that contains (in contrast to **1**) an additional methyl group at its

(1) Parts of this investigation were presented at the 11th International Conference of Organic Process Research & Development, Barcelona, Spain, April 25−28, 2005, and at the XVI Fechem Conference on Organometallic Chemistry, Budapest, Hungary, September 3−8, 2005.

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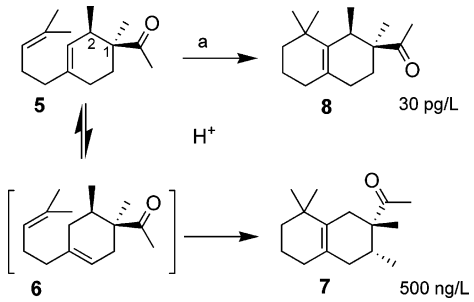
SCHEME 2. Givaudan Synthesis of Georgywood from Precursor 5[a]



[a] Reagents and conditions: (a) H_3PO_4, toluene, 115 °C, 1 h, 74%.[9]

C(2) position.[8] Phosphoric acid-catalyzed cyclization yielded the isomers **7** and **8** in about equal amounts. As an olfactory agent Georgywood **8** was by a factor of >10 000 more powerful than **7** (Scheme 2).[9]

The formation of regioisomer **7** can be explained by a preisomerization of the endocyclic double bond of **5**, giving intermediate **6**, that readily undergoes cyclization to **7** (Scheme 2). Steric constraints between the methyl group at C(2) and the methyl groups of the 4-methylpent-4-enyl side chain of **5** were thereby circumvented, in contrast to Ohloff's cyclohexenes **1** (Scheme 1, R = alkyl), where such a preisomerization was much less predominant.[5,7] The cyclization of a 1,5-diene such as **5**, where the new bond at C(3) of the cyclohexene ring must be formed despite steric constraints of a substituent at C(2), is unique in the literature dealing with polyprenoid cyclization reactions,[2,4,5] and has only recently been attempted on the trans-diastereomer of **5**.[10]

Because the elegant, warm-woody, sweet-powdery smelling Georgywood represents an important alternative to the classic Iso-E Super **2b** in perfumery applications,[6] alternative syntheses of **8** were reported, e.g., by Piancatelli et al.[11] The enantiomers of Georgywood **8** have been synthesized at Givaudan[12] and by Corey et al.[13] Here we communicate our investigations that avoid the preisomerization from **5** to **6** and result in a highly regioselective cyclization of precursor **5** to β-Georgywood **8**.[14]

TABLE 1. Cyclization of Precursor 5 Promoted by Brønsted Acids[d]

entry	acid	equiv (molar)	solvent	temp [°C]	time [h]	yield [%][a]	ratio **7/8**
1	85% H_3PO_4	0.1	xylene	145	1	88	38:62
2	99% H_3PO_4	1.5	toluene	120	0.5	87	41:59
3	polyphosphoric acid	0.1[b]	xylene	145	1.5	86	43:57
4	H_3PO_3	0.1	xylene	145	1	85	45:55
5	65% HPO_3	0.1	xylene	145	24	84	54:46
6	96% H_2SO_4	0.1		110	20	89	66:34
7	Me-P(O)$(OH)_2$	0.6		140	20	80	64:26
8	H_2SO_4/Ac_2O	1/1	HOAc	125	0.5	58	71:29
9	Amberlite H^+	5[b]	xylene	145	48	70[c]	71:29
10	Ph-P=O$(OH)_2$	0.4		130	15	78[c]	72:28
	PhO-P=O$(OH)_2$	1.2		130	4	70[c]	74:26
11	CF_3CO_2H	0.2	toluene	100	2.5	65	76:24
12	MsOH	0.2	toluene	100	2.5	77	76:24
13	Nafion-H	0.3[b]		100	120	76[c]	76:24
14	TosOH	0.2	toluene	100	3.5	78	78:22
15	HCO_2H	6	HCO_2H	50	129	81	78:22

[a] Products isolated by Kugelrohr distillation. [b] Weight equivalents. [c] GC-conversions. [d] Representative assortment of ca. 80 experiments.

Results and Discussion

Brønsted Acid-Promoted Cyclization. At the onset of our investigations, the cyclization of **5** was screened with organic or inorganic Brønsted acids at different temperatures and concentrations. The influence of solvents, emulsifiers, or phase-transfer catalysts was also checked, as well as pyrolysis over different supports at temperatures up to 500 °C. Representative experiments that gave good cyclization yields are listed in Table 1. Selectivities in favor of β-Georgywood **8** over the undesired isomer **7** were observed only in those cases where phosphorous acids were employed (Table 1, entries 1−5).

An important question was whether or not regioisomer **7** was formed from Georgywood **8** under the above-mentioned conditions (Scheme 2). Such a conversion would proceed via ring opening of **8** to **5** (1,5-diene retrocyclization), and equilibration of **7** and **8** consistent with the reversibility of cationic 1,5-diene cyclizations.[15]

In a control experiment using H_3PO_4, we observed a slowly increasing ratio of the product mixture **7**/**8** upon prolonged heating. Isolation and structure elucidation of byproduct **9** explained the erosion of the isomer ratio under these conditions (Scheme 3), which is probably due to a higher instability of **8** relative to **7**. Similarly substituted ethers have been obtained from related precursors under the same conditions,[16] with the crucial carbocationic cyclization of γ,δ-unsaturated carbonyl compounds described by Baldwin.[17]

At high temperatures (150 °C) and with pure Georgywood **8** as substrate, a slow conversion to isomer **7** (12% in 48 h) was observed. We conclude that, at normal cyclization temperatures (100−120 °C) with H_3PO_4 (Table 1, entries 1 and 2), the mixture

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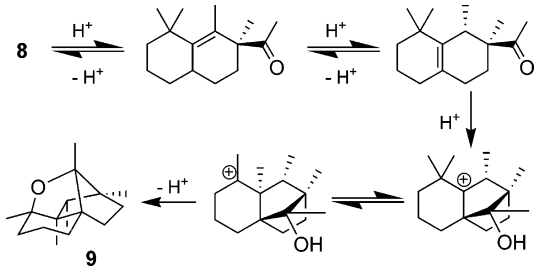
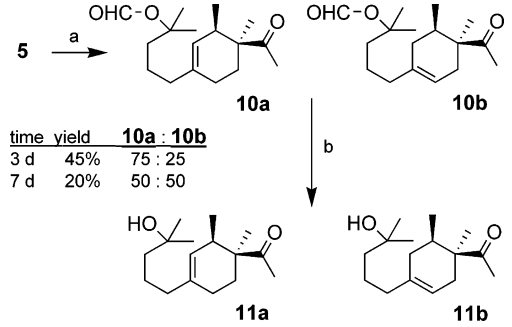
SCHEME 3. Formation of Byproduct 9 from 8[a]



[a] Reagents and conditions: **7**/**8** (1:1), 1 equiv of H_3PO_4, 100 °C, 48 h, 10% (GC/MS).

SCHEME 4. Formic Acid Addition to Precursor 5[a]



[a] Reagents and conditions: (a) HCO_2H, 3−7 d, 25 °C, 40%. (b) MeOH, cat. NaOMe, 1.5 h, 25 °C, 50%.

7/**8** is formed directly from pre-equilibrium **5** ↔ **6** and does not further interconvert.

Preisomerization of **5** to **6** (Scheme 2) at the beginning of the cyclization reactions was followed by GC. The accumulation ($k_1 > k_3$) of **6** was with some acids hardly detectible but with others very pronounced. In the H_2SO_4-catalyzed cyclization reaction (Table 1, entry 6) quenching at the highest concentration of **6** allowed preparative GC separation and NMR analysis of this intermediate.

When the formic acid-promoted cyclization (Table 1, entry 15) was carried out at lower temperatures, the formate adducts **10** were isolated (Scheme 4) and characterized as their alcohols **11**. Because all Brønsted acids should be capable of covalently blocking the sterically less hindered acyclic double bond with different addition and re-elimination rates,[18] such an effect can favor the isomerization of the cyclohexenyl double bond (for a possible neighboring effect of the acetyl group in this pre-isomerization, see Figure 3 and Scheme 11).[19]

(18) (a) Markovnikov addition of formic acid to trisubstituted double bonds and re-elimination: Baird, K. J.; Grundon, M. F.; Harrison, D. M.; Magee, M. G. *Heterocycles* **1981**, 713−717. (b) Addition of phosphoric acid: Julia, M.; Mestdagh, H.; Rolando, C. *Tetrahedron* **1986**, *42*, 3841−3849. HX addition and re-elimination was observed by us when bubbling HCl or HBr through precursor **5** (GC/MS), where after attempted isolation of these halides the partially isomerized mixtures **7**, **8** were obtained after chromatography or distillation.

(19) This hypothesis represents so far the best answer to the important question, why Brønsted acids induce preisomerization and strong, active LA's do not. We also considered an inductive deactivation of the cyclohexenyl double bond depending on the strength of the carbonyl group/acid complex. Although we could not find a well-proven precedent for a deactivation over three σ-bonds, such an effect cannot be excluded.

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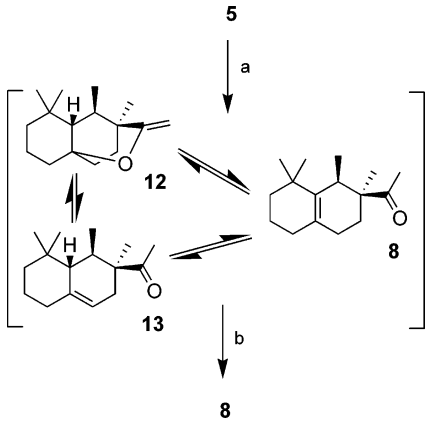
BBr_3	>>	BCl_3	≥	BF_3
$AlBr_3$	•	$AlCl_3$	>>	*AlF_3*
$ZrCl_4$	•	*$ZrBr_4$*	>	*ZrF_4*
$TiCl_4$	≥	$TiBr_4$	>>	TiF_4
$FeCl_3$	>	*$FeBr_3$*	>>	FeF_3
$SnCl_4$	>	*$SnBr_4$*	≈	*SnF_4*
$ZnCl_2$	>>	*$ZnBr_2$*	>>	ZnF_2

FIGURE 2. Classification of type MX_n Lewis acids (X = F, Cl, Br) by reactivity and selectivity toward β-isomer **8**, enol ether **12**, and γ-isomer **13**. Lewis acids giving isomers of this mixture are shadowed. Lewis acids with strong β-Georgywood **8** preference are shown in bold. Lewis acids shown in italic gave larger amounts or predominantly isomer **7**. The other Lewis acids were ineffective. 1.5 equiv of Lewis acid in toluene, xylene, cyclohexane, dichloromethane, or nitroalkanes between 0 and 25 °C, except for BBr_3 at −50 °C.

SCHEME 5[a]



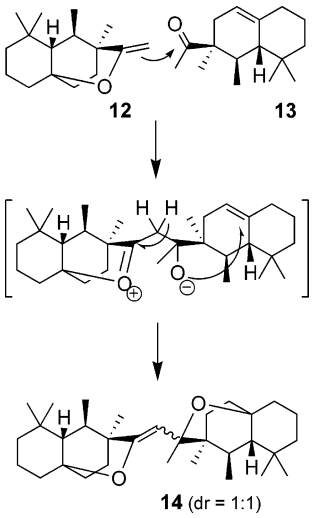
[a] Reagents and conditions: (a) > 1 equiv of MX_n, between −50 and 25 °C, several hours, 40−60% (dist). MX_n = BBr_3, BCL_3, gaseous BF_3, $AlBr_3$, $AlCl_3$, $ZrCl_4$, $TiCl_4$ or $TiBr_4$ in toluene, CH_2Cl_2 or nitropropane, workup. (b) 0.2 equiv of pTSA, toluene, 100 °C, 4 h, 72% (dist).

It is interesting that H_3PO_4 (Table 1, entry 1) gave the best **8**/**7** selectivities (i.e., 62:32) at high temperatures. Further improvements, however, were not possible and other Brønsted acid systems promoted also the unwanted shift of the endocyclic double bond of **5**. With the goal of avoiding this preisomerization, screening experiments with aprotic cyclization reagents, e.g., Lewis acids, were examined next.

Cyclization reaction promoted by MX_n-Type Lewis Acids. To overcome complex formation with the carbonyl group or solvent, more than 1 equiv of a Lewis acid was employed in noncomplexing solvents. Under these conditions we were gratified to obtain a mixture containing mainly **8**, **12**, and **13** in varying amounts (Scheme 5) using strong MX_n-type Lewis acids (Figure 2, shadowed). The Georgywood isomers **12** and **13** were isolated by preparative GC, and their structures were elucidated by NMR in C_6D_6. In these mixtures, the β- and γ-isomers **8** and **13** were the main components. The corresponding α-isomer was not detected.[10c]

In contrast to the Brønsted acid-promoted cyclization, which needed temperatures of at least 80−100 °C (Table 1), the corresponding Lewis acid-promoted cyclization occurred readily at 25 °C or below *and gave for the first time no iso-Georgywood*

SCHEME 6. Formal Mechanism for the Formation of Dimer 14 from 12 and 13[a]



[a] An analogous tentative mechanism can be designed for the formation of **14** from **12** and **8**.

7! The absence of this compound verified our hypothesis that Lewis acids would activate selectively the exocyclic double bond of **5** for cyclization, thus circumventing preisomerization to **6**.

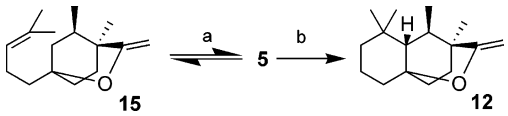
BBr_3, $AlBr_3$, and $ZrCl_4$ (Figure 2, bold) gave the best selectivities for the β-isomer **8**, which were, unfortunately, not perfectly reproducible. When <1 equiv of these Lewis acids (Figure 2, shadowed) was employed, temperatures of above 100 °C were necessary to achieve cyclization. Isomer **7**, derived from preisomerized intermediate **6**, was again the main cyclization product. Catalytic or stoichiometric amounts of metal triflates $M(O_2CCF_3)_n$ or mesylates $M(O_3SCF_3)_n$ were ineffective. Alcoholates such as $Al(OEt)_3$, $Ti(OEt)_4$, and ($iPrO_3TiCl$) did not promote cyclization, but gave partial reduction of the carbonyl group instead. Typical weak Lewis acids such as LiCl or $MgCl_2$ and some of the metal fluorides (Figure 2) gave no conversion at all.

Enol ether **12** and γ-isomer **13** are unstable and convert to β-Georgywood **8** during aqueous acidic workup, over silica, during distillation and even in acidic $CDCl_3$. For preparative purposes, the product mixture of **8**, **12**, and **13** was converted to the desired β-isomer **8** with catalytic amounts of pTSA in toluene (Scheme 5). On the other hand, pure β-Georgywood **8** was reconverted to enol ether **12** with 1.5 equiv of $AlCl_3$ in toluene. These results indicate that the equilibrium among **8**, **12**, and **13** is determined by the Lewis acid reagent (system) and is accompanied by side reactions such as cyclization, dimerization, or polymerization. A quantitative conversion of the isomeric mixture **8**, **12**, and **13** to β-isomer **8** was not achieved.

Upon standing at ambient temperature for several weeks, a crystalline precipitate was collected from the distilled mixtures of **8**, **12**, and **13** and was characterized by NMR as dimer **14** (Scheme 6). Dimer **14** was also detected in the mass spectra of the distillation residues. This explains the inferior yields obtained from the MX_n cyclization, and also why increased amounts of enol ether **12** in the crude product mixtures correlated with decreased amounts of product after distillation.

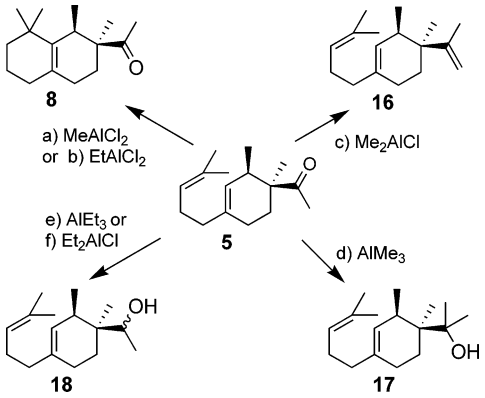
Intramolecular enol ether **15** was normally detected in amounts of less than 10% but was formed as the main product during the $FeCl_3$-promoted cyclization of **5**. Prolonged reaction

SCHEME 7. Enol Ether 15 from Precursor 5 and Further Conversion to Enol Ether 12[a]



[a] Reagents and conditions: (a) 1.5 equiv of $FeCl_3$ in toluene, 25 °C, 1.5 h. (b) Same conditions but 30 h. **12** was contaminated by the β- and γ-isomers **8** and **13** according to Scheme 5.

SCHEME 8. Screening of Alkylaluminum Chlorides R_nAlCl_m[a]



[a] Reagents and conditions: (a) 2 equiv of $MeAlCl_2$, hexane, 16 h, 75 °C, 86% (dist). (b) 2 equiv of $EtAlCl_2$, toluene, hexane, 9 d, 25 °C, 54% (dist). (c) 3 equiv of Me_2AlCl, hexane, 70 °C, 30 d, 30% (FC). (d) 1.5 equiv of $AlMe_3$, 4 h, 60 °C, 93% (dist). (e) 2 equiv of $AlEt_3$, toluene, hexane, 15 h, 25 °C, 94% (dist). (f) 1.5 equiv of Et_2AlCl, toluene, hexane, 2 d, 60 °C, 90% (dist).

times converted **15** further to **12**, probably via **5** as intermediate (Scheme 7).

6-Membered endocyclic enol ethers (3,4-dihydropyrane type) have been selectively obtained through cyclization of γ,δ-unsaturated ketones in the presence of electrophilic reagents (Lewis acids), e.g., from Geranylacetone.[4c] One example of a 6-membered exocyclic enol ether, obtained through Lewis acid-promoted cyclization of γ,δ-unsaturated ketones, has been mentioned.[21]

Cyclization promoted by Alkylaluminum Chlorides, Especially $MeAlCl_2$. During the search for an "ideal cyclization reagent", organometallic homologues of the MX_n-type Lewis acids (Figure 2, shadowed) were tested, to minimize the tendency of these Lewis acids to induce postequilibration (Scheme 5). The systematic screening of alkylaluminum reagents R_nAlX_m was very rewarding (Scheme 8), and β-Georgywood **8** was obtained in excellent yield and selectivity by using stoichiometric amounts ($\geq$2 equiv) of methylaluminum dichloride ($MeAlCl_2$), the first alkyl homologue of $AlCl_3$. For the next higher homologue, ethylaluminum dichloride, the window between effective cyclization temperature and undesired polymerization was narrowed considerably, and with di- or trialkylaluminum compounds, other reactions predominated, resulting from the reducing ability or the higher nucleophilicity of the alkyl substituents. Organoaluminum alkoxides were similarly ineffective: $MeOAlCl_2$ gave predominantly **7** and methylaluminoxane (MAO) converted substrate **5** to **17** under more drastic conditions, as observed also with $AlMe_3$.

(21) Baddeley, G.; Heaton, B. G; Rasburn, J. W. *J. Chem. Soc.* **1960**, 4713 −4719. As in our case (**12**, **15**) the formation of an endocyclic enol ether was not possible, due to the fully substituted endocyclic α-position.

Whereas >1 equiv of the "active" MX_n-type Lewis acids (Figure 2, shadowed) was necessary to obtain Georgywood **8** and its isomers **12** and **13**, ≥2 equiv of the alkylaluminum dihalides $MeAlCl_2$ and $EtAlCl_2$ was needed to achieve a quantitative and clean cyclization of **5** to **8**. Less than 2 equiv of the alkylaluminum dichlorides gave decreased reaction rates and increased side reactions such as polymerization or decomposition, e.g., to 1,1,7-trimethyltetraline. The use of ≥2 equiv of $MeAlCl_2$ provided β-Georgywood **8** in excellent yield (86%) and purity (92%, GC). Less than 0.3% iso-Georgywood **7** was detected and less than 2% of the isomers **12** and **13**.

A less expensive and more readily available Lewis acid than $MeAlCl_2$ was still desired. The use of ≥2.5 equiv of the corresponding sesquichloride $Me_3Al_2Cl_3$ promoted the selective cyclization of **5** to **8** nearly as well (70 °C, 2 h, >70% yield) as 2.5 equiv of $MeAlCl_2$ (Scheme 8). Because $Me_3Al_2Cl_3$ is a complex of 1 equiv of$MeAlCl_2$ × 1 equiv of Me_2AlCl,[22] the use of 2.5 equiv of $Me_3Al_2Cl_3$ would give twice as much aluminum waste and an even higher amount of gaseous methane after quenching the reaction.

Because $MeAlCl_2$ was by far the best Lewis acid for the synthesis of **8** from **5**, we have recently disclosed a procedure for the preparation of $MeAlCl_2$ and its use in the subsequent cyclization of **5** that has the advantage that the pyrophoric $MeAlCl_2$ is prepared and destroyed in one vessel.[14] To elucidate the unique role of the reagent $MeAlCl_2$, however, an in-depth mechanistic study of this reaction was undertaken.

Mechanistic Investigations. The Lewis acids that promote the cyclization of **5** to **8** and its isomers **12** and **13** (Figure 2) correlate partially with the criteria "strong" or "active" established by of Pearson[23] and others.[24,25] The most striking difference between the different acid families employed was that enol ether **12** was detected only in the presence of MX_n-type Lewis acids, but not during or after the Brønsted acid- or $RAlCl_2$-promoted (R = Me, Et) cyclization. However, cyclization transition state **19**, which could lead to enol ether **12**, is possible with every acid employed. A σ-orbital of the carbonyl-oxygen overlaps with the π-orbitals of the cyclohexenyl alkene, which in turn overlap with the π-orbitals of the exocyclic double bond (Figure 3). This would give the carbon framework of Georgywood **8** and its enol ether **12** under stereoelectronic control.

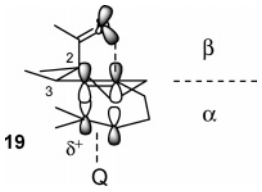
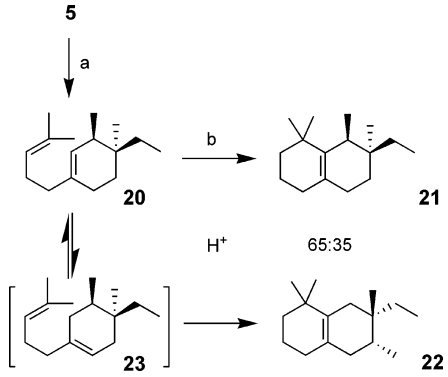


FIGURE 3. Transition state **19** for the cyclization of precursor **5**. Q = H^+ or Lewis acid.

When the $MeAlCl_2$-promoted cyclization of **5** to **8** was run in an NMR tube, no intermediate was observed. Not surprisingly, the carbonyl groups of **5** and **8** were complexed by an aluminum species, as evidenced by the shift of acetyl signals from ~2 to 3 ppm (^{1}H NMR) and from ~210 to 245 ppm (^{13}C NMR).

SCHEME 9. Cyclization of Carbonyl-Free Hydrocarbon 20[a]



[a] Reagents and conditions: (a) Hydrazin hydrate, NaOH, digly, 195 °C, 7 h (95%). (b) cat. H_3PO_4, 145 °C, 14 h (75%).

The same NMR experiment was not possible with the heterogeneous H_3PO_4 cyclization reaction. Consequently, we removed the carbonyl group of **5** by Wolff−Kishner reduction (Scheme 9). Hydrocarbon **20** gave, after H_3PO_4-promoted cyclization, the isomers **21**/**22** in nearly the same good ratio as the one of **7**/**8** obtained from the corresponding cyclization reaction with precursor **5** (Table 1, entry 1), but only after a very prolonged reaction time. From this, we conclude that a pre-equilibrium **20** ↔ **23** exists in analogy to that of **7** ↔ **8** (Scheme 2).

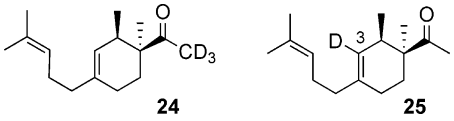


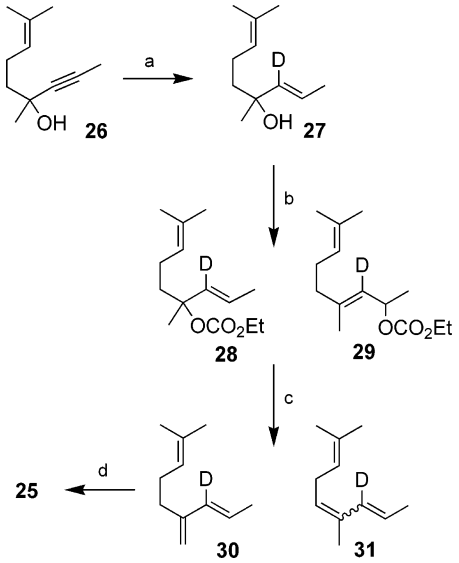
FIGURE 4. Deuterated precursors **24** and **25**. D-grades >95%.

To gain further insight into the mechanism, the deuterated precursors **24** and **25** were prepared (Figure 4). Ketone **24**, fully deuterated at the acetyl group, was prepared from **5** by using K_2CO_3 in D_2O. Precursor **25** was prepared with a deuteration grade of >95% and in good yields from alkynol **26** (Scheme 10).[26] Deuterium was introduced by hydroxy group-assisted selective LAD-deuteration[27] giving allyl alcohol **27**, which was converted to the (partially rearranged) carbonates **28** and **29** (isomer ratio 2:1) that were subjected to a palladium-catalyzed 1,4-elimination to give, via the same η^3-allylpalladium transition state, the dienes **30** and **31** (isomer ratio 3:1). In this mixture, only the reactive diene **30** underwent an endo-selective Diels−Alder reaction with methylisopropenyl ketone to give the cyclization precursor **25** in analogy to the reported Givaudan procedure.[9]

The deuterated precursors **24** and **25** were cyclized with the representative acids H_3PO_4, BBr_3, and $MeAlCl_2$. Regarding the H_3PO_4-catalyzed cyclization of **24**, no insights different from those from previous observations (Scheme 2) were obtained.

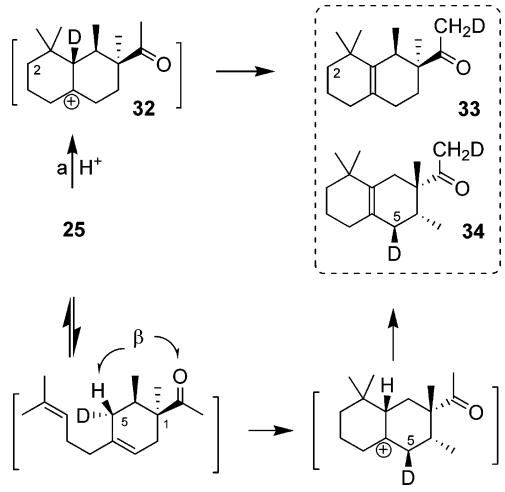
(22) Brandt, J.; Hoffmann, E. G. *Brennst. Chem.* **1964**, *7*, 200−206.
(23) (a) Pearson, R. G. Hard and Soft Acids and Bases. *J. Am. Chem. Soc.* **1962**, *85*, 3533−3539. (b) Santelli, M.; Pons, J.-M. *Lewis acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996.
(24) Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448−7461.
(25) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491−3494.
(26) Pasedach, H. DE 2228333, BASF, 1972 [*Chem. Abstr.* *142*, 219409z]. Alkynol **26** also can be prepared from Dehydro-β-linalol (CAS 29171-20.-8) by using the 3-step procedure described by Glänzer: Glänzer, B. I.; Faber, K.; Griengl, H. *Tetrahedron* **1978**, *43*, 5791−5796.
(27) Damm, L. G.; Hartshorn, M. P.; Vaughan, J. *Aust. J. Chem.* **1976**, *29*, 1017−1021.

SCHEME 10. Synthesis of the Deuterated Precursor 25[a]



[a] Reagents and conditions: (a) $LiAlD_4$, THF, 65 °C, 3 h, 80%. (b) BuLi, hexane, 25 °C, then −50 °C, $ClCO_2Et$, 25 °C, 90%. (c) 100 °C, 0.35 mol % dppe, 0.14 mol % $Pd(OAc)_2$, 30 min, 65%. (d) Methyl isopropenyl ketone, toluene, cat. BF_3OEt_2, 0 °C, 2 h, 85%.

SCHEME 11. Cyclization of the Deuterated Precursor 25 with the Brønsted Acid H_3PO_4[a]

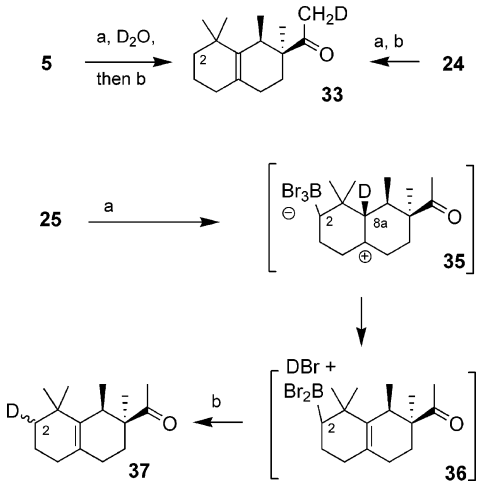


[a] Reagents and conditions: (a) 3−8% H_3PO_4, xylene, 145 °C, 1 h, 70%. Isomer ratio **33**/**34** = 60:40. Epimer ratio at C(5) of **34** = 82:18, D-grade at C(5) of **34** ∼75%. D-grade at the acetyl groups of **33** and **34** <25%. Error of the D-grades ±15% (^{13}C NMR analysis).

Only the deuterium of the acetyl group was partially washed out and reintroduced (at C(2) of **33**) due to enolization. The H_3PO_4-catalyzed cyclization of **25** deserves additional comment, because of the interesting fact that the configuration at C(5) of **34** (Scheme 11) arises from preferential protonation at C(3) of **25** from the more hindered β-face. This outcome is guided by the carbonyl group or an intramolecular enol ether intermediate (deuterated analogue of **15**).[28] This would explain the faster reaction rate in the cyclization of **5** than that of the deoxygenated precursor **20** (Scheme 9). The partial deuterated acetyl groups

(28) We cannot exclude that backside shielding of the α-face of **25** by the isohexenyl side chain, probably favored by π-stacking (in analogy to Figure 3), is solely responsible for this preference.

SCHEME 12. Cyclization of the Precursors 5, 24, and 25 with the MX_n-Type Lewis Acid BBr_3[a]



[a] Reagents and conditions: (a) 1.5 equiv of BBr_3, toluene, −50 °C, 7 h. (b) 0.2 equiv of pTSA, toluene, 100 °C, 4 h, ca. 50% (dist). D-grade of **37** ∼40%. Epimer ratio at C(2) of **37** ∼1:1. D-grade of **33** ∼50%. Error of the D-grades ±15% (^{13}C NMR analysis). The boron intermediates **35** or **36** also can be present as higher complexes, e.g., dimers.

of **33** and **34** arise from D^+ abstraction from intermediate **32** and enolization.

Cyclization of the deuterated precursors **24** and **25** with the representative MX_n-type Lewis acid BBr_3 gave a β-, γ-, and enol ether isomer mixture (deuterated analogues of **8**, **12**, and **13**) that was converted with pTSA to the Georgywood analogues **33** and **37**, respectively (Scheme 12), to allow a better analysis of the deuterated positions by ^{13}C NMR. The deuterium at C(2) of **37** may result from an intermediate C(2)−boron bond as in **35** or **36** that gives after (an intermolecular) deuterium quench the C-2 epimers of **37** in equal amounts. The relatively low deuteration grade in **33** and **37** can be explained by enolization during reaction or workup.[29]

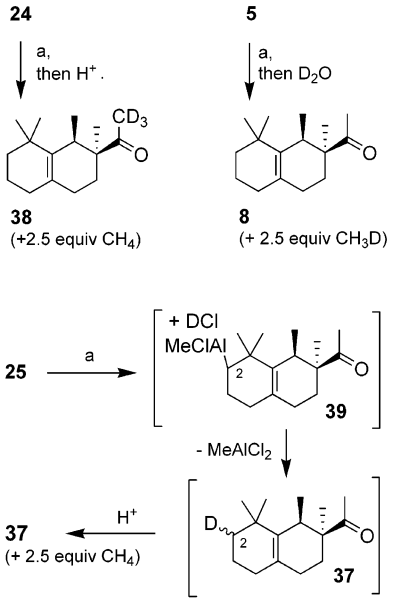
No enolization at all occurs with $MeAlCl_2$ (Scheme 13), in contrast to the cyclization with H_3PO_4 or BBr_3, based on the fact that **38** was obtained without any deuterium loss from **24** after H^+ quench. Accordingly, nondeuterated **8** was obtained from **5** after D_2O quench. The C(2)−Al bond of **39**, which is more basic than the Al−Me bond, was presumably quenched by DCl, as discussed for BBr_3 (Scheme 12). In the complex formation with the acetyl group, $MeAlCl_2$ is a weaker Lewis acid than the strong MX_n-type Lewis acids (Figure 2).[30] Accordingly, no methane evolved during cyclization, but exactly 2.5 equiv (100%) was collected after an aqueous quench of the reaction mixture. The 2.5 equiv of CH_3D obtained after D_2O quench of the **5** → **8** reaction mixture and the 2.5 equiv of nondeuterated methane obtained after H^+ quench of the **24** → **38** or **25** → **37** mixtures confirmed our observations. This result showed also that 2.5 equiv of unaltered $MeAlCl_2$ was present after cyclization and no other species (i.e., Al−CH_2−Al would have given CH_2D_2).[31]

(29) According to the enolization equilibrium RCOMe + MX_n ↔ $RC(=CH)_2OMX_{n-1}$ + HX, Brønsted acid HBr can be generated from precursor **25** and BBr_3.

(30) Strong Lewis acids are capable of enhancing the acidities of α-carbonyl-protons by 20−25 pK_a units: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924−1942. (b) Ren, H.; Cramer, C. J.; Squires, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 2633−2634.

(31) Anet, F. L.; O'Leary, D. J. *Tetrahedron Lett.* **1989**, *30*, 2755−2758.

SCHEME 13. Cyclization of the Precursors 5, 24, and 25 with $MeAlCl_2$[a]



[a] Reagents and conditions: (a) 2.5 equiv of $MeAlCl_2$, hexane, 2 h, 70 °C, 80%. D-grade of **38** >95%. D-grade of **8** 0%. Epimer ratio at C(2) of **37** ~1:1. D-grade of **37** >65%. The aluminum intermediate **39** also can be present as higher complex, e.g., as dimer.

The relevance of the above deuteration experiments can be summarized as follows:

(a) Brønsted acids such as H_3PO_4 induce enolization and preisomerization. The acetyl group seems to assist preisomerization (Scheme 11).

(b) Enolization occurs also with MX_n-type Lewis acids (Scheme 12). The intermediate C(2)−B bond is quenched during reaction (**36** → **37** in Scheme 12).

(c) $MeAlCl_2$ gives no enolization. This explains why no postisomerization and fewer side reactions occur with this reagent (Scheme 13). The intermediate C(2)−Al bond is quenched during reaction (**39** → **37** in Scheme 13).

(d) No other aluminum species arise from $MeAlCl_2$. It remains unchanged after cyclization (Scheme 13) and raises the possibility of a catalytic version of this reaction.

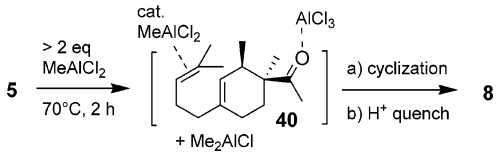
Cyclization with Catalytic Amounts of $MeAlCl_2$ and Its Mechanism. Similar C−C-coupling reactions have been reported that require 2 equiv of $MeAlCl_2$ per carbonyl group,[32] e.g., certain intermolecular Diels−Alder reactions[33] or carbocationic cyclization reactions of unsaturated carbonyl compounds.[34] Snider proposed that carbonyl groups trigger the disproportionation of $MeAlCl_2$,[34a] as is known to happen in the presence of other donor molecules (eq 1).[35] Evidence for this carbonyl-induced disproportionation was noted in the behavior of $MeAlCl_2$ in the presence of methyl benzoate.[36]

$$\text{donor} + 2RAlCl_2 \rightarrow R_2AlCl + [\text{donor}\cdot AlCl_3] \quad (R = Me, Et) \quad (1)$$

If one considers the disproportionation of $MeAlCl_2$ in the presence of precursor **5**, the following conclusions must be drawn (Scheme 14):

(a) The 1 equiv of Me_2AlCl generated is superfluous waste, because Me_2AlCl cannot promote the cyclization of **5** under these conditions (e.g., to **16**, Scheme 8).

SCHEME 14. Disproportionation of >2 equiv of $MeAlCl_2$ in the Presence of Precursor 5 and Complex Formation of $AlCl_3$ and $MeAlCl_2$ with the Lewis Basic Sites of 40[a]



[a] The aluminum species of **40** also can be also present as higher complexes, e.g., dimers.

(b) Any $AlCl_3$ formed in such a disproportionation should preferentially complex with the carbonyl group, because $AlCl_3$ gives a stronger Lewis acid−carbonyl complex than Me_2AlCl or $MeAlCl_2$ (eq 2).[37] The carbonyl group would be preferred as a complexing partner over the less electron-donating double bonds of **5** (eq 3), as confirmed in the above cyclization experiment with >2 equiv of $MeAlCl_2$ in an NMR tube.

$$AlCl_3 > MeAlCl_2 > Me_2AlCl > AlMe_3 \quad \text{(strength of the Lewis acids)} \quad (2)$$

$$R(CO)Me \gg \text{exocyclic C=C} > \text{endocyclic C=C} \quad \text{(strength of Lewis basic basic sites in 5)} \quad (3)$$

(c) The $MeAlCl_2$ left over from disproportionation catalyzes the desired cyclization.

On the basis of these suppositions, it should be possible to effect the cyclization of **5** by adding ~1 equiv of $AlCl_3$ together with catalytic amounts of $MeAlCl_2$. As a prerequisite for this endeavor, precursor **7** is fortunately inert in the presence of ≤1 equiv of $AlCl_3$ up to 100 °C. With >1 equiv of $AlCl_3$, as shown above, surplus $AlCl_3$ accelerates the cyclization at 25 °C but also induces postisomerization. The necessity of ≤1 equiv of $AlCl_3$ per carbonyl group, which decreases the activity of this Lewis acid by complex formation, is also known in certain Diels−Alder reactions, where polymerization was observed with ≥1 equiv of $AlCl_3$.[38] In the optimized realization of this idea (Table 2, entry 4), 0.95 equiv of $AlCl_3$ and 0.15 equiv of

(32) The use of ≥2 equiv of $MeAlCl_2$/carbonyl group in C−C-coupling reactions is not mandatory. Ca. 1 equiv or catalytic amounts of $MeAlCl_2$ have also been used successfully in reactions such as Cycloalkylation, intramolecular Diels−Alder, epoxide-initiated cation−olefin cyclization, aldol condensation, carbocationic cyclization of unsaturated carbonyl compounds, and carbonyl ene reactions. See, for example: (a) Abouabdellah, A.; Bonnet-Delpon, D. *Tetrahedron* **1994**, *50* 11921−11932. (b) Rogers, C.; Keay, B. *Can. J. Chem.* **1993**, *71*, 611−622. (c) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005−7008. (d) Naruse, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Chem. Lett.* **1985**, 1451−1452. (e) Goeke, A.; Mertl, D.; Brunner, G. *Angew. Chem., Int. Ed.* **2004**, *44*, 99−101.

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(34) (a) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 153−157. (b) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538−4545. (c) Karras, M.; Snider, B. B. *J. Am. Chem. Soc.* **1980**, *102*, 7951−7953. (d) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872−5880. See also ref 32e.

(35) (a) Lehmkuhl, H.; Ziegler, K. In *Houben-Weyl, Methoden der organischen Chemie*; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1970; pp 51−55, 59−78, and 95−101 and refs 2−5 on p 71. (b) Tarao, R.; Takeda, S. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 650−655. (c) Lehmkuhl, H.; Kobs, H. D. *Tetrahedron Lett.* **1965**, *29*, 2505−2510.

(36) Starowieyski, K. B.; Pasynkiewicz, S.; Sporzynski, A. *J. Organomet. Chem.* **1976**, *117*, 117−128.

(37) See, for example: Smith, C. A.; Wallbridge, G. H. *J. Chem. Soc. A* **1967**, 7−12.

(38) Inukai, T.; Michio, K. *J. Org. Chem.* **1965**, *30*, 3567−3569.

TABLE 2. Cyclization of Precursor 5 Promoted by Different $AlCl_3$/$MeAlCl_2$ Combinations[a,b]

entry	$AlCl_3$ [equiv]	$MeAlCl_2$ [equiv]	effective[c] $MeAlCl_2$ [equiv]	temp [°C]	time [h]	yield[d] of **8** or other products	purity
1	0.95			55	18	**6**, **7**, **8**	1:1:1
2	0.5	0.25		55	18	**5**, **6**	1:1
3	0.95	0.1	0	65	sluggish conversion		
4	*0.95*	*0.15*	*0.05*	*55*	*18*	*61%*	*77%*
5	0.95	0.25	0.15	65	2	65%	74%
6	0.9	0.5	0.3	40	7	72%	71%
7	0.8	0.9	0.5	60	1	70%	80%
8		2.5	0.5	70	2	80%	92%

[a] Substrate **5** and reagents (in toluene) mixed at −20 °C. [b] 55 °C, 20 h, H^+-quench. [c] $MeAlCl_2$ leftover for activation of the exocyclic double bond after disproportionation according to eqs 1−3 and Scheme 14. [d] Yield (after distillation) corrected by purity.

TABLE 3. In Situ Generation of Catalyst $MeAlCl_2$ from $AlMe_3$[a,b]

entry	$AlCl_3$ [equiv]	$AlMe_3$ [equiv]	effective $MeAlCl_2$ [equiv][c]	effective $AlCl_3$[d] [equiv]	time [h]	yield[e] of **8** or other products	purity [%]
1	1.05			1.05	24	mixture of **5**, **6**, **8**, **15**	
2	*1.05*	*0.05*	*0.05*	*1.0*	*24*	*69%*	*84*
3	1.1	0.1	0.1	1.0	24	56%	73
4	0.95	0.3		0.8	24	low conversion	
5	1.1	0.3		0.95	24	not reproducible	
6	1.6	0.8	0.4	1.0	4	70%	87

[a] $AlCl_3$, $AlMe_3$, toluene, 100 °C, 1 h. [b] Addition of substrate **5** at −10 °C, then 55 °C, 20 h, H^+ quench. [c] $MeAlCl_2$ leftover for activation of the exocyclic double bond after disproportionation of the employed $AlMe_3$ according to eqs 1−4 and Scheme 14. [d] $AlCl_3$, generated according to eqs 1−4, that is partially or completely consumed for complex formation with the carbonyl group. [e] Yield (after distillation) corrected by purity.

$MeAlCl_2$ effected the cyclization of **5** to β-isomer **8** in good yield (83%).

Without $MeAlCl_2$ under otherwise identical conditions, preisomerization of **5** to **6** was observed (Table 2, entry 1). The cyclization also does not take place properly with $AlCl_3$/$MeAlCl_2$ combinations, where after $MeAlCl_2$ disproportionation and complexing $MeAlCl_2$ is no longer available for activation of the exocyclic double bond (Table 2, entries 1−3). In the case where $MeAlCl_2$ is available for this activation (Table 2, entries 4−8), the cyclization rate increases as more catalyst is left over for cyclization. The reaction, however, works best with >2 equiv of $MeAlCl_2$ alone (Table 2, entry 8). Once again the higher alkyl homologues of $MeAlCl_2$ (Scheme 8) could not replace $MeAlCl_2$, consistent with the catalytic role of $MeAlCl_2$ (Scheme 14) and inconsistent with $MeAlCl_2$ solely providing water-free conditions for an $AlCl_3$-promoted cyclization.

$AlMe_3$-Catalyzed Cyclization. It was known that $MeAlCl_2$ can be generated from $AlCl_3$ and $AlMe_3$ (eq 4),[35a] but we were pleased when we could use this equilibrium also in the presence of donor molecules such as the carbonyl group of **5** for the in situ generation of $MeAlCl_2$.

$$AlMe_3 + 2AlCl_3 \leftrightarrow 3MeAlCl_2 \qquad (4)$$

After optimization, the combination $AlCl_3$/$AlMe_3$ worked as well as the previous combination $AlCl_3$/$MeAlCl_2$ (Table 3, entry 2).

Because 1 equiv of $AlMe_3$ should generate 3 equiv of $MeAlCl_2$ in the presence of an excess of $AlCl_3$ (eq 4), even less $AlMe_3$ could be employed than $MeAlCl_2$. The cyclization was blocked or not reproducible (Table 3, entries 3 and 4) when more than 0.1 equiv of $AlMe_3$ was used. This is understandable if one considers disproportionation and complexing as discussed above, with the consequence that no $MeAlCl_2$ is available for activation of the exocyclic double bond. The combination of 1.6 equiv of $AlCl_3$ and 0.8 equiv of $AlMe_3$, which should generate 2.4 equiv of $MeAlCl_2$ in situ, gave similar results (Table 3, entry 5) as 2.5 equiv of $MeAlCl_2$ alone (Table 2, entry 8). Without catalyst $AlMe_3$, preisomerization, and enolization occurred as expected (Table 3, entry 1).

Summary. Pre-equilibration of the endocyclic double bond of cyclization precursor **5**, which occurs in the presence of Brønsted acids, was avoided by using the organoaluminum reagent, $MeAlCl_2$. This also circumvented postequilibration of the carbocationic cyclization product, which occurred in the presence of MX_n-type Lewis acids. β-Georgywood **8** was obtained with high selectivity and good yields with use of $MeAlCl_2$ in stoichiometric or even catalytic amounts. Both versions presumably proceed via carbonyl blocking effected by $AlCl_3$ generated from $MeAlCl_2$. Stoichiometric amounts of $AlCl_3$ have to be added, if $MeAlCl_2$ is used catalytically. The catalyst $MeAlCl_2$ can also be generated in situ from $AlMe_3$. Although the yield of the catalytic version is slightly lower than the stoichiometric reaction, the process advantages are obvious: less pyrophoric reagent, less aluminum waste, and less generation of gaseous methane. It can be expected that $AlCl_3$ carbonyl blocking and catalytic $MeAlCl_2$ activation will also find its application in similar C−C coupling reactions that were previously carried out with stoichiometric amounts of $MeAlCl_2$.

Experimental Section

1-(*cis*-1,2,3,4,5,6,7,8-Octahydro-1,1,7,8-tetramethylnaphthalen-7-yl)ethanone (8). For the preparation of cyclization precursor **5** see refs 8 and 9. Analytical data for **8**: ^{1}H NMR δ 0.85 (d, 3 H, J = 6.9 Hz), 0.99 (s, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.4−2.2 (10 H), 2.15 (s, 3 H,), 2.36 (q, 1 H, J = 6.9 Hz). ^{13}C NMR δ 19.15 (t), 19.7 (q), 21.1 (q), 22.5 (t), 24.9 (q), 27.7 (t), 28.4 (q), 29.4 (q), 30.8 (t), 34.0 (s), 35.4 (d), 40.1 (t), 50.7 (s), 125.9 (s), 136.95 (s), 214.5 (s). MS (EI) *m*/*z* (%) 234 (M^+, 25), 219 (15), 191 (100), 161 (20), 135 (65), 121 (40), 105 (40), 91 (30). IR (film) ν 2930 (m), 1700 (s), 1460 (m), 1377 (m), 1357 (m), 1240 (w), 1220 (w), 1090 (m) cm^{-1}. HRMS calcd for $C_{16}H_{26}O$: 234.1984. Found: 234.1981. For further analytical data, see ref 12b.

Method A: H_3PO_4 (85%, 10 g, 85 mmol) is added dropwise to precursor **5** (200 g, 0.85 mol) in xylene (200 g) at 145 °C. After 2 h at this temperature, the reaction mixture is cooled to 20 °C and treated with 0.5% aqueous Na_2CO_3. Phase separation, extraction of the aqueous phase with xylene, washing of the organic phase to pH 7, drying over $MgSO_4$, filtration, and evaporation of the solvent gives an oily residue, which is short-path distilled. After addition of 24 g of paraffin to the distillate (202 g) and a second distillation (30 cm, glass coil) 184 g of a **7**/**8** mixture (84% purity, ratio 40:60) is obtained at 105 °C/0.1 mbar. Yield of **8** corrected by purity: 45%.

Method B: Precursor **5** (2 g, 8.5 mmol) in toluene (10 mL) is cooled under nitrogen and stirring to −50 °C, where BBr_3 (3.2 g, 13 mmol) is added dropwise via syringe. After 7 h at −50 °C, 2 M HCl is added at this temperature. Warmed again to 25 °C, the mixture is extracted with *tert*-butyl methyl ether. The organic phase is washed with concentrated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Bulb-to-bulb distillation at 130 °C/0.1 mbar gives 1.1 g of a **8**/**12** mixture, which is dissolved in toluene (5 mL) and treated with *p*-toluenesulfonic acid (40 mg, 0.2 mmol). After 4 h at 100 °C the organic phase is washed with Na_2CO_3 and water until pH 7, dried, and concentrated under reduced pressure giving 1.2 g of a brown oil, which is bulb-to-bulb distilled at 120 °C/0.05 Torr giving 0.8 g (40%) of **8** with ∼90% purity.

Method C: γ-Georgywood **13** (1.3 g, 5.6 mmol) and *p*-toluenesulfonic acid (0.25 g, 1.4 mmol) in toluene (3 mL) are stirred for 4 h at 100 °C. After cooling to 20 °C the organic phase is washed with Na_2CO_3 and water until pH 7, dried, and concentrated under reduced pressure. Bulb-to-bulb distillation gives 0.95 g (47%) of **8** with ~90% purity.

Method D: Precursor **5** (20 g, 85 mmol) in toluene (100 g) is added under ice cooling to methylaluminum dichloride (1 M in hexane, 157 g, 0.21 mol). The mixture is heated to 70 °C for 2−3 h, then quenched under ice-cooling with ethanol (40 g), then with 2 M HCl. The organic phase is separated and the aqueous phase extracted with *tert*-butyl methyl ether. The combined organic layers are washed with concentrated NaCl, then with water until pH 7. The organic phase is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue is distilled giving 16 g (80%) of β-Georgywood **8** at 124 °C/0.1 Torr as a colorless liquid and with a purity of ~90% according to GC and NMR.

Method E: Precursor **5** (15 g, 64 mmol) in toluene (60 g) is added at −10 °C to a suspension of anhydrous $AlCl_3$ powder (8.4 g, 61 mmol) in toluene (25 mL) under nitrogen and stirring. After addition of methylaluminum dichloride (9.6 g, 9.6 mmol) in hexane (1 M), the brown-red solution is heated at 55 °C for 18 h. The solution is poured upon ice/water (300 g) and extracted with hexane. The combined organic layers are washed with $NaHCO_3$ and water until pH 7, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue (18 g) is purified by bulb-to-bulb distillation, giving 10 g of β-Georgywood **8** (61%) at 125 °C/0.1 Torr with a GC purity of 87% according to GC and NMR.

Method F: $AlCl_3$ powder (9 g, 67 mmol) and $AlMe_3$ (2 M in heptane, 1.6 mL, 3 mmol) in toluene (25 mL) are heated under nitrogen and stirring to 100 °C. After 1 h at this temperature, the suspension is cooled to −10 °C, where precursor **5** (15 g, 64 mmol) in toluene (60 g) is added within 30 min. The solution is stirred at 55 °C for 24 h, then cooled to room temperature, poured upon ice/water (200 mL), and extracted with hexane. The combined organic layers are washed with $NaHCO_3$ and water until pH 7, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue (16.1 g) is purified by bulb-to-bulb distillation giving 11.8 g of β-Georgywood **8** (69%) at 125 °C/0.1 Torr with a GC purity of 84%.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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