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Dehydrogenative Nucleophilic Addition of Aliphatic Ether to Benzaldehyde Dimethyl Acetal Mediated by Ether–Boron Trifluoride (1/1) Affording 1-Alkoxy-2-alkylindenes or α,β-Unsaturated Carbonyl Compounds Specifically

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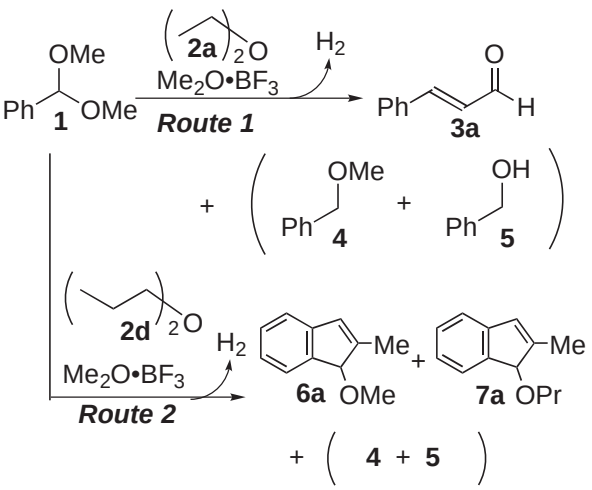
The $R_2O \cdot BF_3$-mediated dehydrogenative crossed aldol condensation reaction of acyclic aliphatic ethers with benzaldehyde dimethyl acetal to give specifically indene derivatives or α,β-unsaturated carbonyl compounds has been found. When the ethers have bis(β-alkylethyl) ether structures, dehydrogenative formation of enol ether equivalents followed by successive crossed aldol addition to acetal-originated electrophile and intramolecular electrophilic aromatic substitution reactions give annulation products of 1-alkoxy-2-alkylindenes. When the ether has two β- and one or more α-hydrogens, α,β-unsaturated carbonyl compounds are obtained. The structural correlation between deuterated starting materials and the obtained products, the structural requirements for ethers, and the distinct substrate specificity have revealed the reaction routes and mechanisms.

We have been investigating the acid-mediated decarbonylative diarylation reaction of α-alkoxy- and α-oxocarboxylic acids, where the α-carbon of the carboxylic acids act as equivalents of those of highly activated aldehydes or ketones.[1] During the course of the investigation, we have unexpectedly found that diethyl ether (Et_2O, **2a**) reacts with benzaldehyde dimethyl acetal (**1**) in the presence of $Me_2O \cdot BF_3$ to afford cinnamaldehyde (**3a**) (Scheme 1, Route 1). We have ascertained that some aliphatic ethers yield similarly α,β-unsaturated carbonyl compounds. A part of the results have been reported preliminarily.[2] Recently, we have found that the reaction of dipropyl ether [$(n\text{-Pr})_2O$, **2d**] with acetal **1** affords a pair of annulation products, 1-methoxy-2-methylindene (**6a**)[3] and 2-methyl-1-propoxyindene (**7a**), in place of α,β-unsaturated carbonyl compounds (Scheme 1, Route 2). We have ascertained that several ethers also undergo this unique annulation. The production of indene derivatives **6** and **7**, and α,β-unsaturated carbonyl compound **3** from ethers accompanies distinct specificity.



Scheme 1.

In this paper, we wish to report and discuss the overall reaction behavior, the structural requirements, and the reaction mechanisms in the specific transformation of aliphatic ethers with benzaldehyde dimethyl acetal into indene derivatives and α,β-unsaturated carbonyl compounds.

Results and Discussion

The Reaction Behaviors of Aliphatic Ethers 2 with Benzaldehyde Dimethyl Acetal (1) in the Presence of $Me_2O \cdot BF_3$. The results of the reaction of benzaldehyde dimethyl acetal (**1**) with/without Et_2O (**2a**) in the presence of $R_2O \cdot BF_3$ are shown in Table 1.

The reaction of acetal **1** with Et_2O (**2a**) in the presence of $Me_2O \cdot BF_3$ afforded cinnamaldehyde (**3a**) and benzyl methyl ether (**4**) with the evolution of H_2 (Entry 1). On the other hand,

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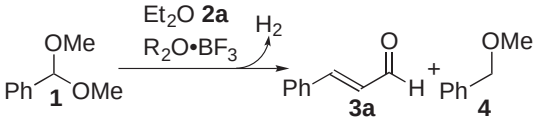
benzaldehyde (**8**) did not react with Et_2O (**2a**) (Entry 2). Furthermore, the reaction of benzaldehyde dimethyl acetal (**1**) with $Me_2O{\cdot}BF_3$ in the absence of Et_2O (**2a**) gave no adducts (Entry 3). In contrast, acetal **1** reacted with $Et_2O{\cdot}BF_3$ yielding cinnamaldehyde (**3a**) without the addition of Et_2O (**2a**). Consequently, Et_2O (**2a**) is proved to form cinnamaldehyde (**3a**) on the condition that benzaldehyde dimethyl acetal (**1**) and $Me_2O{\cdot}BF_3$ are present. The existence of acetal is apparently crucial to accomplish this transformation.

Table 1. Reaction of Benzaldehyde Dimethyl Acetal (**1**) with/without Et_2O (**2a**) in the Presence of $R_2O{\cdot}BF_3$[2,a)]



Entry	Acetal or equivalent	**2a**/ mmol	$R_2O{\cdot}BF_3$	H_2[b)]	Product distribution/%[c)]		
					3a	**4**	**8**
1	**1**	20	$Me_2O{\cdot}BF_3$	+	12	16	72
2	PhCHO (**8**)	20	$Me_2O{\cdot}BF_3$	−	—	—	100
3	**1**	0	$Me_2O{\cdot}BF_3$	−	—	2	98
4	**1**	0	$Et_2O{\cdot}BF_3$	+	43	40	17

a) Reaction conditions: acetal **1** or benzaldehyde (**8**), 2 mmol; $R_2O{\cdot}BF_3$, 12 mmol; CH_2Cl_2, 20 mL; 25 °C, 3 h, under a N_2 atmosphere. b) Evolution of H_2 was confirmed by gas detector tube; GASTEC Corporation, Gas Detector Tube No. 30; sign plus denotes evolution of H_2 and minus denotes not. c) Calculated on the basis of ^{1}H NMR spectrum.

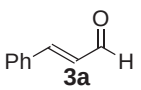
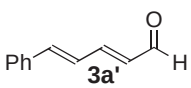
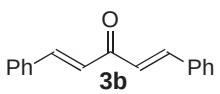
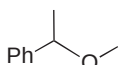
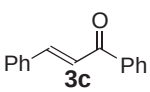
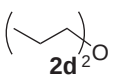
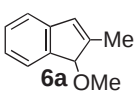
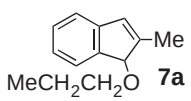
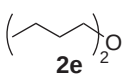
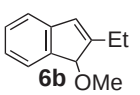
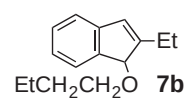
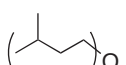
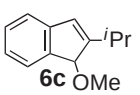
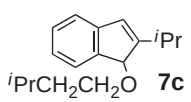
Table 2 shows the results of the reaction of several aliphatic ethers **2** with benzaldehyde dimethyl acetal (**1**) in the presence of $Me_2O{\cdot}BF_3$.

When Et_2O (**2a**), diisopropyl ether [$(i\text{-Pr})_2O$, **2b**], or methyl 1-phenylethyl ether (**2c**) was allowed to react with acetal **1**, α,β-unsaturated carbonyl compounds **3a**–**3c** were formed with the evolution of H_2. At the same time, formation of benzyl methyl ether (**4**) and/or benzyl alcohol (**5**) was observed (Entries 1–3).[2]

In contrast to the production of α,β-unsaturated carbonyl compounds **3**, some kinds of ethers have been found to yield annulated products specifically under the same conditions. As shown in Entries 4–6 of Table 2, the treatment of $(n\text{-Pr})_2O$ (**2d**), dibutyl ether [$(n\text{-Bu})_2O$, **2e**], or diisopentyl ether (**2f**) with acetal **1** did not yield α,β-unsaturated carbonyl compounds **3**. Instead, mixtures of pairs of homologues of indene derivatives, i.e. 1-methoxyindenes **6** and 1-(β-alkylethoxy)-indenes **7**, were obtained. In these reactions, H_2 was formed with benzyl methyl ether (**4**) and benzyl alcohol (**5**). Unlike the reaction of the acyclic ethers, treatment of THF (**2g**) with acetal **1** did not give α,β-unsaturated carbonyl compounds **3** or indene derivatives **6** and **7** (Entry 7).

The formation of the indene skeleton has been confirmed by the X-ray crystal structure determination of 1,2-dibromo-

Table 2. Reaction of Aliphatic Ethers **2** with Benzaldehyde Dimethyl Acetal (**1**) in the Presence of $Me_2O{\cdot}BF_3$[a)]

Entry	Ether **2**	H_2[b)]	Product distribution/%[c)]						
			α,β-Unsaturated carbonyl compounds or indene derivatives				**4**	**5**	**8**
1[2]	 **2a**	+	 **3a**	19	 **3a'**	9	52	12	8
2[2]	 **2b**[2]	+	 **3b**	59			31	8	2
3[2,d)]	 **2c**	+	 **3c**	27			14	0	59
4	 **2d**[2]	+	 **6a**	31	 **7a**	16	34	10	9
5	 **2e**	+	 **6b**	45	 **7b**	20	18	11	6
6	 **2f**	+	 **6c**	33	 **7c**	11	35	5	16
7[2]	 **2g**	−	—				24	0	76

a) Reaction conditions: benzaldehyde dimethyl acetal (**1**), 0.5 mmol; ether **2**, 5 mmol; $Me_2O{\cdot}BF_3$, 3 mmol; 25 °C, 3 h, in the N_2 atmosphere. b) Evolution of H_2 was confirmed by gas detector tube; GASTEC Corporation, Gas Detector Tube No. 30; sign plus denotes evolution of H_2 and minus denotes not. c) Calculated on the basis of ^{1}H NMR spectrum. d) CH_2Cl_2 (5 mL) was added as solvent.

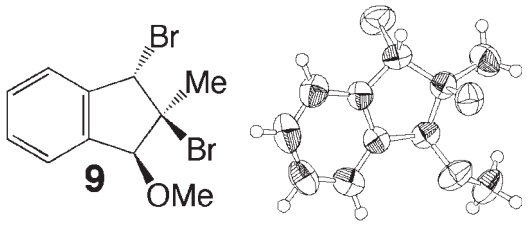
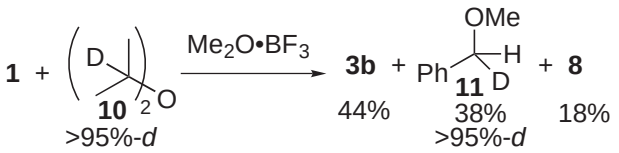


Fig. 1. X-ray crystal structure of 1,2-dibromo-3-methoxy-2-methylindane (**9**).



Scheme 2.

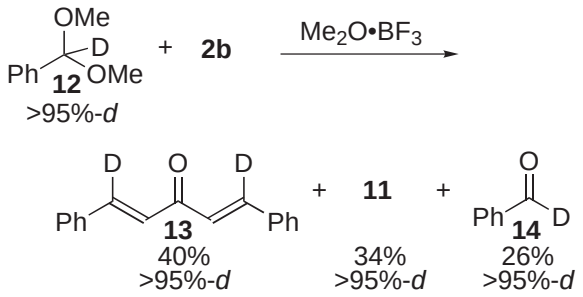
3-methoxy-2-methylindane (**9**), which was obtained as the dibrominated adduct of one of the products in the reaction of $(n\text{-Pr})_2O$ (**2d**) with acetal **1** (Fig. 1).

There have been several reports on the preparation of indene derivatives.[4–7] However, formation of 1-alkoxyindenes by annulation between acetal and ether has never been reported.

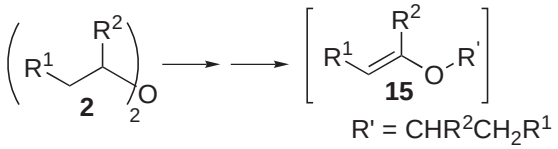
The Reaction Mechanisms of the Dehydrogenative Transformation of Aliphatic Ethers into Enol Ether Equivalents. As described above, distinct specificity is observed in the formation reaction of 1-alkoxy-2-alkylindenes **6** and **7** or α,β-unsaturated carbonyl compounds **3** from aliphatic ethers **2** and benzaldehyde dimethyl acetal (**1**). In the first place, the acyclic ether structure is required to form these products. When the alkyl group of the ether has a bis(β-alkylethyl) ether skeleton [$(R^1CH_2CH_2)_2O$], 1-alkoxyindene derivatives **6** and **7** are obtained predominantly. On the other hand, Et_2O (**2a**) or α-substituted ethyl ethers **2b** and **2c** gave α,β-unsaturated carbonyl compounds **3** in the $Me_2O\cdot BF_3$-mediated reaction with acetal **1**.

α,β-Unsaturated carbonyl compounds are generally synthesized by crossed aldol-type condensations. Actually, treatment of benzaldehyde dialkyl acetals with vinyl ethers in the presence of Lewis acids affords cinnamaldehyde homologues.[8] Consequently, the formation of α,β-unsaturated carbonyl compounds **3a**–**3c** from acetal **1** and aliphatic ethers **2a**–**2c** indicates that ethers are oxidized to enol ether equivalents in the early stages of this transformation system. In this course, H_2, benzyl methyl ether (**4**), and benzyl alcohol (**5**) are surely yielded by the action of hydride species formed in this oxidation step. As formation of indene derivatives from ethers accompanies the evolution of H_2, and the formation of benzyl methyl ether (**4**) and benzyl alcohol (**5**), indene derivatives are yielded presumably via at least a partially common reaction pathway, i.e. oxidative transformation of ethers into enol ether equivalents.

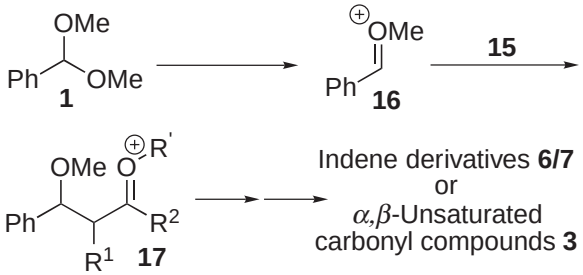
The proposed mechanism is supported by the results of the reaction of deuterated substrates. The $Me_2O\cdot BF_3$-mediated reaction of α-deuterated diisopropyl ether [bis(1-deuterio-1-methylethyl) ether, **10**] with acetal **1** in the presence of $Me_2O\cdot BF_3$ has been found to afford a non-deuterated α,β-unsaturated carbonyl compound **3b** and α-monodeuterated benzyl methyl ether (**11**) (Scheme 2). This result indicates that the α-hydrogen (deuterium) of the ethers is oxidatively eliminated as a hydride (deuteride), and a part of the hydrides (deuterides) react with acetal **1** to form benzyl methyl ether (**4** and **11**).



Scheme 3.



Scheme 4.



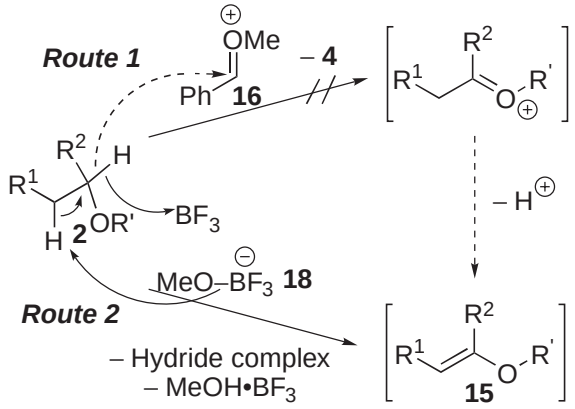
Scheme 5.

In addition, when α-deuterated acetal **12** was allowed to react with ether **2b**, a β-deuterated α,β-unsaturated carbonyl compound **13** and α-monodeuterated benzyl methyl ether (**11**) were obtained (Scheme 3). This result shows that the hydride source in this reaction is ether **2b**. The α-hydrogen of the acetal does not function as a hydride source in contrast to the acid-mediated Cannizzaro reaction.[9]

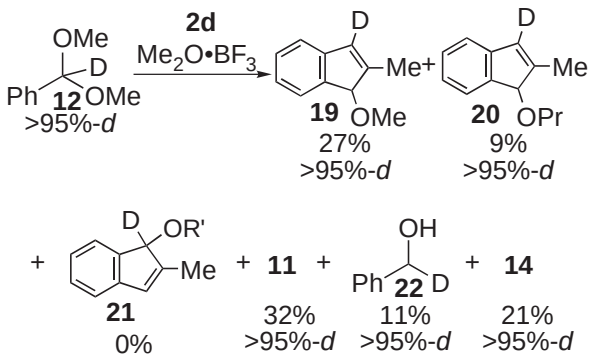
Consequently, saturated aliphatic ethers **2** are certainly transformed dehydrogenatively into enol ether equivalent species like structure **15** (Scheme 4). The enol ether equivalent readily reacts with the electrophiles such as alkoxycarbenium ion **16** to afford 1-alkoxy-2-alkylindenes **6** and **7**, or α,β-unsaturated carbonyl compounds **3** via precursors **17** (Scheme 5).

For the dehydrogenative transformation of aliphatic ethers to enol ether equivalents depicted in Scheme 4, there are two possible routes (Scheme 6). One is the hydride abstraction from ether **2** by alkoxycarbenium ion **16**, followed by proton release giving benzyl methyl ether (**4**) and an enol ether equivalent species (Route 1). The other is the hydride abstraction by dissociated free BF_3 followed by proton release (Route 2).

Because the evolution of H_2 indicates that the reaction of a hydride and a proton advances in this system, direct capture of hydride from alkyl ether **2** by alkoxycarbenium ion **16** to give benzyl methyl ether (**4**) shown in Route 1 (Scheme 6) is incon-



Scheme 6.



Scheme 7.

sistent with the formation of H_2. In addition, if the reaction proceeded via Route 1, the sum of benzyl methyl ether (**4**) and benzyl alcohol (**5**) should be always larger than the amount of 1-alkoxy-2-alkylindenes **6** and **7** or α,β-unsaturated carbonyl compounds **3**. From this point, the product distribution shown in Entries 2–6 of Table 2 reconfirms the favor of Route 2.

In Route 2, dissociated free BF_3 abstracts a hydride from aliphatic ether **2**. This hydride abstraction is probably achieved in cooperation with proton abstraction by BF_3-methoxide complex (**18**) that is formed from the reaction of dissociated BF_3 and acetal **1**. As a result of abstraction of a proton and hydride, $MeOH \cdot BF_3$ and the hydride complex are formed. The hydride complex thus formed in situ reacts with a proton source to generate H_2, or attacks an alkoxycarbenium ion to form benzyl methyl ether (**4**). In addition, benzyl alcohol (**5**) probably yields after formation of benzyl methyl ether (**4**) via cleavage of the carbon–oxygen linkage.

Consequently, transformation of ether **2** probably undergoes via Route 2. The distinguished difference in reactivity of acetal **1** and benzaldehyde (**8**) strongly supports the involvement of BF_3-methoxide complex (**18**), which is only formed from acetal **1** (Table 1, Entries 1 and 2).

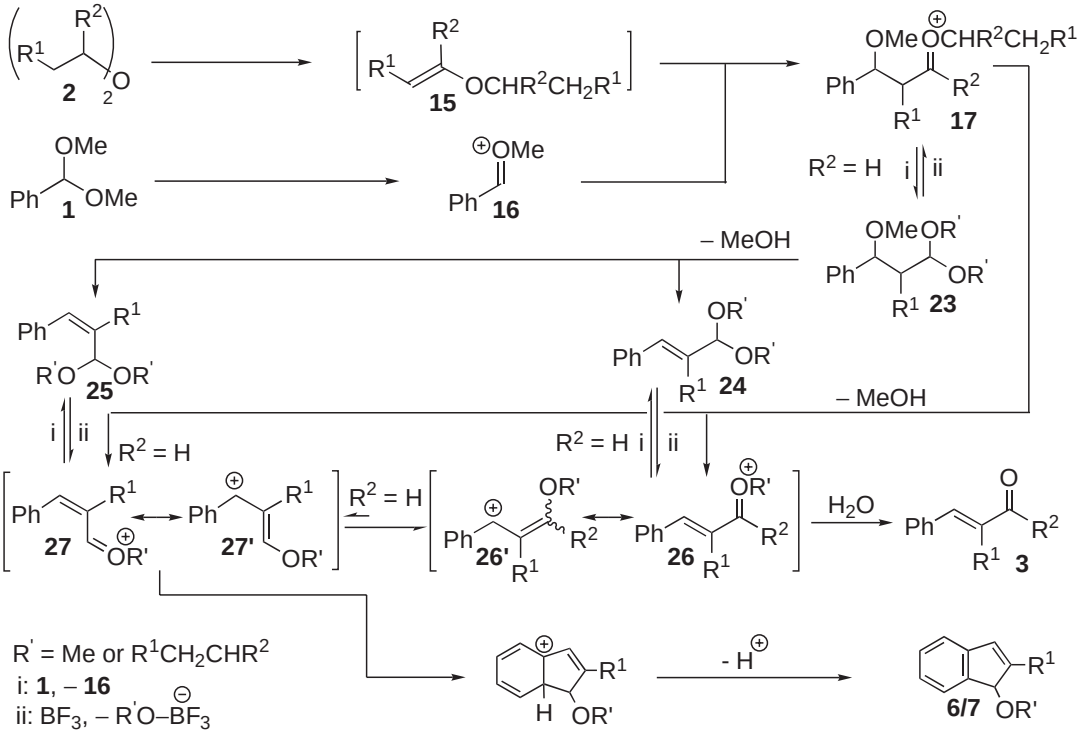
To the best of our knowledge, the transformation of aliphatic ethers into enol ether equivalents has never been reported. As the only one related reaction, Arulraj and Alphonse have reported the self-condensation of benzaldehyde dialkyl acetals catalyzed by $Et_2O \cdot BF_3$, where cinnamaldehyde derivatives are formed via disproportionative crossed aldol condensation of an alkoxycarbenium ion formed from the acetal and an enolate equivalent also generated from the alkoxy moiety in the acetal.[10] In their report, the carbon source of cinnamaldehyde derivatives is limited to acetals, and the possibility of ether to react is never considered.

The Reaction Mechanisms for Formation of Two Types of Indene Derivatives. The formation of mixtures of pairs of homologues having different alkoxy groups at the 1-position, i.e. 2-alkyl-1-methoxyindenes **6a–6c** and 2-alkyl-1-(alkylethoxy)indenes **7a–7c** (Entries 4–6 in Table 2), suggests that this annulation accompanies the interchange of the 1-alkoxy groups. However, the $Me_2O \cdot BF_3$-mediated reaction of α-deuterated benzaldehyde dimethyl acetal (**12**) with $(n\text{-Pr})_2O$ (**2d**) afforded 1-alkoxy-3-deuterio-2-methylindenes **19** and **20** (Scheme 7), and did not give 1-alkoxy-1-deuterio-2-methylindenes **21**. Therefore, the 1-positioned carbons of the indene rings in compounds **6** and **7** surely originate in the α-carbon of the employed ether. Consequently, the methoxy group on the 1-positioned carbon of the indene ring in products **6a–6c** necessarily originates in the methoxy group of acetal **1**. Furthermore, the reaction behavior of α-deuterated benzaldehyde dimethyl acetal (**12**) also indicates that the interchange of the alkoxy group occurs during the generation of the indene ring structure and that the S_N2'-type interchange of the alkoxy groups never occurs after formation of the indene skeletons.

The Reaction Pathway of the Specific Formation of 1-Alkoxy-2-alkylindenes or α,β-Unsaturated Carbonyl Compounds. On the basis of the reaction behaviors described above, the interpreted reaction pathway for formation of 1-alkoxy-2-alkylindenes **6** and **7**, and α,β-unsaturated carbonyl compounds **3** from acyclic ether **2** and acetal **1** is demonstrated in Scheme 8.

At the early stage of this transformation, ethers **2** and acetal **1** afford aldol equivalent **17** and the hydride complex with the aid of $Me_2O \cdot BF_3$. If the intermediate **17** does not have potential to form indene derivatives **6** and **7**, only (*E*)-alkoxycarbenium ion **26** or γ-alkoxyallyl cation **26′** forms, resulting in formation of α,β-unsaturated carbonyl compound **3** by work-up treatment. On the other hand, when aldol equivalent **17** is formed from bis(β-alkylethyl) ethers **2d–2f** and acetal **1**, intermediate **17** is further transformed into (*E*)- and (*Z*)-alkoxycarbenium ions **26** and **27**, or their resonance hybrid as γ-alkoxyallyl cations **26′** and **27′** via elimination of methanol. During the equilibrium among carbenium ions **17**, **26**, and **27**, and acetals **23**, **24**, and **25**, an appreciable amount of the intermediates should exchange their alkoxy group with the methoxy group of acetal **1**. The subsequent intramolecular electrophilic aromatic substitution of the generated (*Z*)-alkoxycarbenium ion **27** or its resonance hybrid **27′** affords 1-alkoxy-2-alkylindenes **6** and **7**, which have either of two alkoxy groups, i.e. those originated in acetal **1** ($R' = Me$) or bis(β-alkylethyl) ethers **2d–2f** ($R' = R^1CH_2CH_2$).

The β-alkyl group (R^1) of the ethers **2d–2f** is considered to destabilize the (*E*)-form ion **26**/**26′** and to drive the equilibrium between (*E*)-form ions **26** and **26′**, and (*Z*)-form ions **27** and **27′** toward the latter. Furthermore, the absence of substituents at the α-carbon in the ethers **2d–2f** ($R^2 = H$) is considered to be significant for the progress of the intramolecular electrophilic attack of the oxonium carbon of (*Z*)-cations **27** and **27′**.



Scheme 8.

The ethers that afford α,β-unsaturated carbonyl compounds **3**, i.e. Et_2O (**2a**), $(i\text{-}Pr)_2O$ (**2b**), and methyl 1-phenylethyl ether (**2c**), have a β-unsubstituted ethyl ether structure or α-substituted one. The former structure (ether **2a**; $R^1 = R^2 = H$) predominantly makes the (*E*)-isomer of the intermediates like species **24** and **26**, which is far more stable than the (*Z*)-isomer. The intermediates formed from the latter ethers **2b**/**2c** ($R^2 \neq H$) have the structure of ketone acetals, which is rather unstable compared with those of the corresponding aldehyde acetals **23**/**24**/**25** ($R^2 = H$). For these reasons, the transformation of these ethers presumably terminates before cyclization, giving 1-alkoxy-2-alkylindenes **6** and **7**. As a supporting experimental result, the reaction of bis(1-methylpropyl) ether ($R^1 = R^2 = Me$), an α-alkyl-substituted ether, with acetal **1** has been found to give a complex mixture containing a small amount of the corresponding α,β-unsaturated carbonyl compound **3** without indene derivatives **6** and **7** on the basis of the ^1H NMR spectra.

Conclusion

We have found the BF_3-mediated transformation reaction of aliphatic ethers and benzaldehyde dimethyl acetal to yield 1-alkoxy-2-alkylindenes or α,β-unsaturated carbonyl compounds with distinct specificity. The transformation is initiated by dehydrogenative generation of enol ether equivalents from aliphatic ethers with the aid of $Me_2O{\cdot}BF_3$ and benzaldehyde dimethyl acetal. The enol ether equivalents readily afford α,β-unsaturated carbonyl compound precursors, which further give 1-alkoxyindene derivatives on the condition that the structural requirements are satisfied. Otherwise, the inert enol ether equivalent intermediates formed in situ yield α,β-unsaturated carbonyl compounds. The function of aliphatic ethers as enol ether equivalents for carbon–carbon bond formation is extraordinarily unique. Furthermore, the specific domino oxidation-crossed aldol condensation-electrophilic aromatic substitution type annulation is also a unique behavior of such conventional molecules.

Experimental

General. Aliphatic ethers **2**, $R_2O{\cdot}BF_3$, and CH_2Cl_2 were purchased and purified according to the method in the literature.[11] Acetals **1** and **12** were synthesized according to the method in the literature.[12] Ether **10** was synthesized by the same method in the literature[13] from 2-deuterio-2-propanol. Distillation of indene derivatives was carried out by Kügelrohr distillation. Boiling points were determined by the temperature of the furnace. ^1H NMR spectra were recorded on a JEOL JNM-LA500 (500 MHz) or a JEOL JNM-AL300 (300 MHz) spectrometer using Me_4Si (^1H, δ 0.00) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-LA500 (125 MHz) or a JEOL JNM-AL300 (75 MHz) spectrometer using $CDCl_3$ (^{13}C, δ 77.0) as an internal standard. IR spectra were recorded on a JASCO FT/IR-5300. High-resolution mass spectra (HRMS) were recorded on a JEOL MStation JMS-700. X-ray diffraction measurements were carried out on a Rigaku Rapid.

The Reaction of Aliphatic Ether 2 with Acetal 1 in the Presence of $Me_2O{\cdot}BF_3$. $Me_2O{\cdot}BF_3$ (3 mmol, 0.342 g) was added to a mixture of ether **2** (5 mmol) and acetal **1** (0.5 mmol, 0.076 g) and the solution was stirred at 25 °C for 3 h. The solution was quenched with water (20 mL) and then extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl (15 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

1-Methoxy-2-methylindene (6a).[3] Indene derivative **6a** was isolated by column chromatography (silica-gel, hexane:ethyl acetate = 5:1 v/v) and distillation (15%, pale yellow oil). bp 92–94 °C (8 mmHg). ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, d,

$J = 7.5$ Hz), 7.23 (1H, t, $J = 7.5$ Hz), 7.14 (1H, d, $J = 7.5$ Hz), 7.12 (1H, t, $J = 7.5$ Hz), 6.45 (1H, s), 4.86 (1H, s), 3.05 (3H, s), 2.03 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8 (C), 143.8 (C), 141.7 (C), 128.7 (CH), 128.3 (CH), 124.6 (CH), 123.7 (CH), 120.1 (CH), 84.8 (CH), 51.8 (CH_3), 14.1 (CH_3) ppm. IR ν (neat): 1720, 1626, 1606, 1464, 1373, 1321, 1207, 1107, 1080, 752 cm^{-1}. HRMS m/z (EI) calcd for $C_{11}H_{11}O$ $(M - H)^+$ 159.0810, found 159.0766.

2-Ethyl-1-methoxyindene (6b). Indene derivative **6b** was isolated by column chromatography (silica-gel, hexane:ethyl acetate = 5:1 v/v) and distillation (19%, pale yellow oil). bp 101–102 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, $J =$ 7.5 Hz), 7.23 (1H, t, $J = 7.5$ Hz), 7.14 (1H, d, $J = 7.5$ Hz), 7.12 (1H, t, $J = 7.5$ Hz), 6.46 (1H, s), 4.95 (1H, s), 3.07 (3H, s), 2.5–2.2 (2H, m), 1.21 (3H, t, $J = 6.6$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1 (C), 143.8 (C), 141.8 (C), 128.4 (CH), 126.7 (CH), 124.6 (CH), 123.8 (CH), 120.3 (CH), 83.8 (CH), 51.8 (CH_3), 21.5 (CH_2), 12.4 (CH_3) ppm. IR ν (KBr): 1722, 1618, 1460, 1319, 1203, 1103, 1082, 752, 734 cm^{-1}. HRMS m/z (EI) calcd for $C_{12}H_{13}O$ $(M - H)^+$ 173.0966, found 173.0925.

1-Methoxy-2-(1-methylethyl)indene (6c). Indene derivative **6c** was isolated by column chromatography (silica-gel, hexane: ethyl acetate = 5:1 v/v) and distillation (12%, pale yellow oil). bp 108–110 °C (9 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, $J = 7.5$ Hz), 7.23 (1H, t, $J = 7.5$ Hz), 7.14 (1H, d, $J =$ 7.5 Hz), 7.12 (1H, t, $J = 7.5$ Hz), 6.44 (1H, s), 5.05 (1H, s), 3.07 (3H, s), 2.69 (1H, sep, $J = 6.6$ Hz), 1.22 (3H, d, $J = 6.6$ Hz), 1.20 (3H, d, $J = 6.6$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5 (C), 143.6 (C), 141.8 (C), 128.3 (CH), 126.7 (CH), 124.7 (CH), 123.8 (CH), 120.4 (CH), 82.7 (CH), 51.8 (CH_3), 27.3 (CH), 23.3 (CH_3), 20.6 (CH_3) ppm. IR ν (KBr): 1720, 1618, 1466, 1205, 1107, 1080, 752, 734 cm^{-1}. HRMS m/z (EI) calcd for $C_{13}H_{16}O$ $(M)^+$ 188.1201, found 188.1198.

2-Methyl-1-propoxyindene (7a). Indene derivative **7a** was isolated by column chromatography (silica-gel, hexane:ethyl acetate = 5:1 v/v) and distillation (3%, pale yellow oil). bp 111–114 °C (8 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, d, $J = 7.5$ Hz), 7.22 (1H, t, $J = 7.5$ Hz), 7.13 (1H, d, $J = 7.5$ Hz), 7.11 (1H, t, $J = 7.5$ Hz), 6.42 (1H, s), 4.89 (1H, s), 3.13–3.11 (2H, m), 2.05 (3H, s), 1.56 (2H, sext, $J = 7.3$ Hz), 0.90 (3H, t, $J = 7.3$ Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4 (C), 143.6 (C), 142.5 (C), 128.2 (CH), 128.1 (CH), 124.5 (CH), 123.6 (CH), 120.1 (CH), 84.4 (CH), 66.1 (CH_2), 23.4 (CH_2), 14.2 (CH_3), 10.7 (CH_3) ppm. IR ν (neat): 1718, 1604, 1462, 1319, 1205, 1170, 1105 cm^{-1}. HRMS m/z (EI) calcd for $C_{13}H_{16}O$ $(M)^+$ 188.1201, found 188.1197.

1-Butoxy-2-ethylindene (7b). Indene derivative **7b** was isolated by column chromatography (silica-gel, hexane:ethyl acetate = 5:1 v/v) and distillation (5%, pale yellow oil). bp 120–123 °C (7 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, $J =$ 7.5 Hz), 7.23 (1H, t, $J = 7.5$ Hz), 7.14 (1H, d, $J = 7.5$ Hz), 7.12 (1H, t, $J = 7.5$ Hz), 6.43 (1H, s), 4.96 (1H, s), 3.2–3.1 (2H, m), 2.5–2.2 (2H, m), 1.55–1.45 (2H, m), 1.40–1.32 (2H, m), 1.25 (3H, t, $J = 7.9$ Hz), 0.88 (3H, t, $J = 7.9$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8 (C), 143.6 (C), 142.5 (C), 128.2 (CH), 126.1 (CH), 124.6 (CH), 123.7 (CH), 120.2 (CH), 83.3 (CH), 64.2 (CH_2), 32.3 (CH_2), 21.6 (CH_2), 19.4 (CH_2), 13.9 (CH_3), 12.5 (CH_3) ppm. IR ν (KBr): 1716, 1616, 1466, 1203, 1170, 1107, 1080, 752, 736 cm^{-1}. HRMS m/z calcd for $C_{15}H_{20}O$ $(M)^+$ 216.1514, found 216.1491.

1-(3-Methylbutoxy)-2-(1-methylethyl)indene (7c). Indene derivative **7c** was isolated by column chromatography (silica-gel, hexane:ethyl acetate = 5:1 v/v) and distillation (4%, pale yellow oil). bp 128–130 °C (7 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, d, $J = 7.5$ Hz), 7.23 (1H, t, $J = 7.5$ Hz), 7.14 (1H, d, $J = 7.5$ Hz), 7.12 (1H, t, $J = 7.5$ Hz), 6.42 (1H, s), 5.10 (1H, s), 3.3–3.1 (2H, m), 2.68 (1H, sep, $J = 6.6$ Hz), 1.68 (1H, t, $J = 6.6$ Hz), 1.46–1.40 (2H, m), 1.26 (3H, d, $J = 6.6$ Hz), 1.20 (3H, d, $J = 6.6$ Hz), 0.85 (3H, d, $J = 6.6$ Hz), 0.83 (3H, d, $J = 6.6$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2 (C), 143.4 (C), 142.6 (C), 128.2 (CH), 125.1 (CH), 124.6 (CH), 123.7 (CH), 120.4 (CH), 82.3 (CH), 62.8 (CH_2), 39.1 (CH_2), 27.3 (CH), 24.8 (CH), 23.5 (CH_3), 22.8 (CH_3), 22.4 (CH_3), 20.7 (CH_3) ppm. IR ν (KBr): 1718, 1618, 1460, 1201, 1105, 1082, 752 cm^{-1}. HRMS m/z (EI) calcd for $C_{17}H_{24}O$ $(M)^+$ 244.1827, found 244.1889.

3-Deuterio-1-methoxy-2-methylindene (19). Indene derivative **19** was isolated by column chromatography (silica-gel, hexane:ethyl acetate = 5:1 v/v) and distillation (8%, pale yellow oil). bp 93–96 °C (7 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, $J = 7.5$ Hz), 7.23 (1H, t, $J = 7.5$ Hz), 7.14 (1H, d, $J =$ 7.5 Hz), 7.12 (1H, t, $J = 7.5$ Hz), 4.86 (1H, s), 3.05 (3H, s), 2.03 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 143.8, 141.8, 128.6 (t, $J_{CD} = 28$ Hz), 128.3, 124.6, 123.7, 120.1, 84.8, 51.7, 14.0 ppm. IR ν (KBr): 1720, 1626, 1606, 1464, 1373, 1321, 1207, 1107, 1080, 752 cm^{-1}. HRMS m/z (EI) calcd for $C_{11}H_{11}DO$ $(M)^+$ 161.0951, found 161.0925.

3-Deuterio-2-methyl-1-propoxyindene (20). Indene derivative **20** was isolated by column chromatography (silica-gel, hexane:ethyl acetate = 5:1 v/v) and distillation (3%, pale yellow oil). bp 112–115 °C (8 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, d, $J = 7.5$ Hz), 7.22 (1H, t, $J = 7.5$ Hz), 7.13 (1H, d, $J = 7.5$ Hz), 7.11 (1H, t, $J = 7.5$ Hz), 4.89 (1H, s), 3.20–3.01 (2H, m), 2.05 (3H, s), 1.62–1.51 (2H, m), 0.90 (3H, t, $J = 7.3$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 143.6, 142.5, 128.2 (t, $J_{CD} = 28$ Hz), 128.1, 124.5, 123.6, 120.0, 84.4, 66.1, 23.3, 14.1, 10.7 ppm. IR ν (KBr): 1718, 1604, 1462, 1319, 1205, 1170, 1105 cm^{-1}. HRMS m/z (EI) calcd for $C_{13}H_{15}DO$ $(M)^+$ 189.1264, found 189.1229.

Synthesis of 1,2-Dibromo-3-methoxy-2-methylindane (9). Bromine (4.5 mmol, 0.719 g) was dropped into a solution of 1-methoxy-2-methylindene (**6a**) (4.5 mmol, 0.720 g) in CH_2Cl_2 (40 mL) at 0 °C and stirred for 1 h. The brownish colored solution immediately turned colorless. The solution was quenched with water (50 mL) and extracted with CH_2Cl_2 (40 mL × 3). The combined extracts were washed with saturated aqueous NaCl (30 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. One of the isomers was isolated by repeated silica-gel column chromatography (first, hexane:$CHCl_3$ = 1:1 v/v; second, toluene) of the obtained crude products. The isolated dibromoindane **9** was purified by recrystallization (hexane) three times (8%, colorless prism). mp 56.5–57 °C.

1,2-Dibromo-3-methoxy-2-methylindane (9): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5–7.3 (4H, m), 5.73 (1H, s), 4.52 (1H, s), 3.80 (3H, s), 2.26 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 140.2, 129.4, 128.9, 125.2, 124.5, 88.6, 75.9, 60.4, 60.3, 29.0 ppm. IR ν (KBr): 1712, 1462, 1356, 1201, 1105, 1089 cm^{-1}. Anal. Calcd for $C_{11}H_{12}Br_2O$: C, 41.28; H, 3.78%. Found: C, 41.28; H, 3.78%.

X-ray Crystal Structure Analysis. Diffraction measurements were carried out on a Rigaku AFC5R detector diffractometer equipped with graphite-monochromated Cu Kα radiation ($\lambda =$ 1.5418 Å).

1,2-Dibromo-3-methoxy-2-methylindane (**9**): The crystal suits for structure analysis measured 0.3 × 0.2 × 0.2 mm^3. Indane **9**

crystallized in the monoclinic unit cell, space group $C2/c$, $a = 19.558(5)$, $b = 9.050(3)$, $c = 14.333(3)$ Å, $\beta = 113.315(16)^\circ$, $V = 2329.8(11)$ Å^3, $Z = 8$, $D_{calcd} = 1.825\,Mg\,m^{-3}$, $\lambda = 1.5418$ Å, $\mu = 8.550\,mm^{-1}$, $F(000) = 1248$. Data were collected for $4.92 < \theta < 67.00^\circ$. The structure was solved by a direct method (SIR92)[14] and refined by least squares against F^2 to $R1 = 0.0630$ ($wR2 = 0.1476$) and $S_{goof} = 1.052$. All hydrogen atoms were added with a fixed distance by the SHELXL-97 program.[15]

Crystallographic data for the structures of 1,2-dibromo-3-methoxy-2-methylindane (**9**) in this paper have been deposited with the Cambridge Crystallographic Data Centre: Deposition number CCDC-277928. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Supporting Information

Figures S1–S9 show ^{1}H and ^{13}C NMR spectra of indene derivatives **6**, **7**, **19**, and **20** and dibromoindane **9** in PDF format. This material is available free of charge on the web at: http://www.csj.jp/journals/bcsj/.

References

1 a) N. Yonezawa, Y. Tokita, T. Hino, H. Nakamura, R. Katakai, *J. Org. Chem.* **1996**, *61*, 3551. b) N. Yonezawa, T. Hino, Y. Tokita, K. Matsuda, T. Ikeda, *Tetrahedron* **1997**, *53*, 14287. c) N. Yonezawa, T. Hino, M. Shimizu, K. Matsuda, T. Ikeda, *J. Org. Chem.* **1999**, *64*, 4179. d) N. Yonezawa, T. Hino, T. Kinuno, T. Matsuki, T. Ikeda, *Synth. Commun.* **1999**, *29*, 1687. e) N. Yonezawa, T. Hino, T. Ikeda, *Recent Res. Dev. Synth. Org. Chem.* **1998**, *1*, 213. f) N. Yonezawa, T. Hino, K. Matsuda, T. Matsuki, D. Narushima, M. Kobayashi, T. Ikeda, *J. Org. Chem.* **2000**, *65*, 941. g) A. Kameda, H. Nishimori, S. Omura, M. Koike, T. Hino, T. Jobashi, K. Maeyama, N. Yonezawa, *Nippon Kagaku Kaishi* **2002**, 211. h) T. Jobashi, T. Hino, K. Maeyama, H. Ozaki, K. Ogino, N. Yonezawa, *Chem. Lett.* **2005**, *34*, 860.

2 T. Jobashi, M. Takano, T. Hino, K. Maeyama, K. Fugami, H. Ozaki, K. Ogino, N. Yonezawa, *Chem. Lett.* **2004**, *33*, 1246.

3 a) S. Kapur, N. C. Mathur, K. McManus, A. L. Pincock, J. A. Pincock, *Can. J. Chem.* **1988**, *66*, 2888. b) J. A. Pincock, I. S. Young, *Can. J. Chem.* **2003**, *81*, 1083.

4 a) J. Koo, *J. Am. Chem. Soc.* **1952**, *75*, 2000. b) J. C. Canevet, V. Graff, *Tetrahedron* **1978**, *34*, 1935. c) G. A. Olah, G. Asensio, H. Mayr, *J. Org. Chem.* **1978**, *43*, 1518. d) A. Padwa, T. J. Blacklock, R. Loza, *J. Am. Chem. Soc.* **1981**, *103*, 2404. e) P. G. Karmarkar, V. R. Chinchore, M. S. Wadia, *Synthesis* **1981**, 228. f) A. Padwa, T. J. Blacklock, R. Loza, *J. Org. Chem.* **1982**, *47*, 3712. g) M. G. Steinmetz, R. T. Meyes, *J. Am. Chem. Soc.* **1985**, *107*, 2111. h) L. Anke, P. Weyerstahl, *Chem. Ber.* **1985**, *118*, 613. i) G. Singh, H. Ila, H. Junjappa, *Synthesis* **1986**, 744. j) C. Roussel, H. G. Rajoharison, L. Bizzari, L. Shaimi, *J. Org. Chem.* **1988**, *53*, 683. k) S. Saito, Y. Sato, T. Ohwada, K. Shudo, *J. Am. Chem. Soc.* **1994**, *116*, 2312.

5 a) L. S. Liebeskind, J. R. Gasdaska, J. S. McCallum, S. J. Tremont, *J. Org. Chem.* **1989**, *54*, 669. b) L. G. Quan, V. Gevorgyan, Y. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3545. c) V. Gevorgyan, L. G. Quan, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 4089. d) D. K. Rayabarapu, C.-H. Cheng, *Chem. Commun.* **2002**, 942. e) D. K. Rayabarapu, C.-H. Yang, C.-H. Cheng, *J. Org. Chem.* **2003**, *68*, 6726. f) K.-J. Chang, D. K. Rayabarapu, C.-H. Cheng, *Org. Lett.* **2003**, *5*, 3963. g) K.-J. Chang, D. K. Rayabarapu, C.-H. Cheng, *J. Org. Chem.* **2004**, *69*, 4781.

6 a) M. Lautens, J. Mancuso, *Org. Lett.* **2002**, *4*, 2105. b) M. Lautens, J. Mancuso, *J. Org. Chem.* **2004**, *69*, 3478. c) M. Lautens, T. Marquardt, *J. Org. Chem.* **2004**, *69*, 4607. d) T. Miura, M. Murakami, *Org. Lett.* **2005**, *7*, 3339. e) R. Shintani, K. Okamura, T. Hayashi, *Chem. Lett.* **2005**, *34*, 1294. f) T. Matsuda, M. Makino, M. Murakami, *Chem. Lett.* **2005**, *34*, 1416.

7 M. E. Bos, W. D. Wulff, R. A. Miller, S. Chamberlin, T. A. Brandvold, *J. Am. Chem. Soc.* **1991**, *113*, 9293.

8 a) B. M. Mikhailov, G. S. Ter-Sarkisyan, *Zh. Obshch. Khim.* **1959**, *29*, 1642. b) S. M. Makin, G. A. Ermakova, O. A. Shavrygina, A. P. Pleshkova, V. N. Voznesenskii, *Zh. Org. Khim.* **1979**, *15*, 1852.

9 Y. Okuda, T. Morimoto, Y. Fujita, *Nippon Kagaku Kaishi* **1972**, 1442.

10 a) I. Alphonse, S. J. Arulraj, *Indian J. Chem.* **1985**, 199. b) I. Alphonse, S. J. Arulraj, *J. Indian Chem. Soc.* **1986**, 820.

11 W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, 4th ed., Butterworth-Heinemann, Oxford, **1996**.

12 S. G. Davies, C. L. Goodfellow, *J. Chem. Soc., Perkin Trans. 1* **1990**, 393.

13 J. Hoffner, M. J. Schottelius, D. Feichtinger, P. Chen, *J. Am. Chem. Soc.* **1998**, *120*, 376.

14 SIR92: A. Altomare, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi, G. J. Polidori, *J. Appl. Crystallogr.* **1994**, *27*, 435.

15 G. M. Sheldrick, *SHELXL-97 Program for Crystal Determination and Refinement*, University of Göttingen, Germany, **1997**.