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PAPER

New general synthesis of α-alkoxyketones *via* α′-alkylation, α-alkylation and α,α′-dialkylation of α-alkoxyketimines†

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α-Methoxy- and α-ethoxyketones, as important intermediates in organic synthesis and flavor compounds in food chemistry, were synthesized by deprotonation of *N*-(1-alkoxy-2-propylidene)isopropylamine, prepared by condensation of the corresponding α-alkoxyacetone with isopropylamine, and subsequent reaction of the corresponding 1-azaallylic anions with alkyl halides to afford α′-alkylated, α-alkylated and α,α′-dialkylated ketimines. Hydrolysis of the imino function led to the desired substituted α-alkoxyketones. The ratio of α-, α′-, and α,α′-(di)alkylated compounds depended on the amount of base used and on the nature of the alkylating reagent.

Introduction

α-Alkoxyketones **1–3** (Fig. 1) have long been known as important and versatile building blocks in organic synthesis. These ketones have been used in the synthesis of natural products such as 4-quinoline alkaloids,[1] salviolone,[2] 3-butyl-4-methylenefuran-2(5*H*)-one,[3] and the aggregation pheromone lardolure.[4] They have also been used in the preparation of ring fused pyrazoles as CRF-1 receptor ligands,[5,6] and as GABA-A α2 subtype selective receptor modulators,[7] 4*H*-pyran-4-ones,[8] 5-lipoxygenase inhibitors,[9] phenylpiperazines as melanocortin-4-receptor antagonists,[10] tetrahydroquinolines as analogues of the antiviral compound Virantmycin,[11] and quinolines.[12] α-Methoxyketones have also found application for the study of ester enolate Claisen rearrangements,[13] in enantioselective reductions with catecholborane,[14] and for transformation to enol silyl ethers.[15] α-Alkoxyketones are interesting also in food chemistry,[16] since α-ethoxy- and α-methoxyketones have been identified as flavor compounds of Burgundy Pinot Noir red wines,[17] cognac,[18] pineapple pulp,[19] Jinhua ham,[20] durian,[21] dry-cured ham,[22] and traditional balsamic vinegar,[23] and have been synthesized within an early study on the aroma constituents of sake.[24] One of the oldest and most general methods to synthesize α-alkoxyketones entails addition of Grignard reagents across α-alkoxyacetonitriles.[24,25] Alternative syntheses involve addition of alkoxy-substituted Grignard reagents across amides,[26] oxidation of alkoxyalcohols,[11,27] acid-mediated conversion of dialkoxyalkanols,[28] or epoxy ethers,[29] acid hydrolysis of alkoxy substituted enol ethers,[30] nucleophilic substitution of α-halomethylketimines[31] or α-haloketones[16,32] by sodium alkoxides, hydroboration of alkoxyalkynes,[33] reaction of 1,2-dimethoxyethenyllithium and organoboranes,[34] reaction of 2-methoxy-substituted silylated ketone acetals with carboxylic acid chlorides,[35] reaction of lithiated 1-(α-alkoxyalkyl)benzotriazoles with aldehydes followed by rearrangement,[36] and electrophilic methoxylation of enol ethers.[37] Recently, the regioselective thermodynamically controlled allylation of O-protected hydroxyacetones at the carbon bearing the hydroxy group was accomplished, while alkylation mostly led to disappointing results with unacceptable yields and unsuccessful separation of regioisomers.[38] Very recently, the asymmetric synthesis of (*R*)-3-benzyloxybutanone *via* alkylation of an α-alkoxyacetyl derivative of *N*-1-(1′-naphthyl)-ethyl-*O*-*tert*-butylhydroxylamine was described.[39]

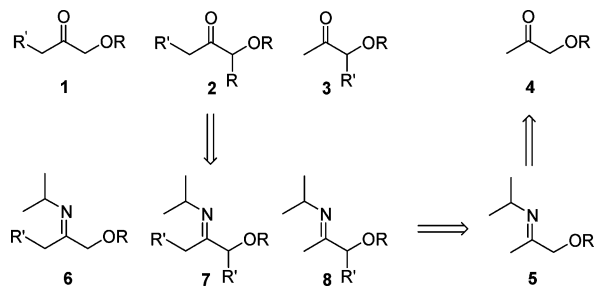

Fig. 1 Retrosynthetic scheme for the synthesis of α-alkoxyketones **1–3** *via* α-, α′- and α,α′-(di)alkylation of α-alkoxyketimines **5** and subsequent hydrolysis of the alkylated α-alkoxyketimines **6–8**.

Despite the many available routes to α-alkoxyketones **1–3**, the coupling reaction of the 1-azaallylic anion derived from an α-alkoxyketimine **5**, accessible from the ketone **4**, with alkyl halides and subsequent hydrolysis of the alkylated α-alkoxyketimines **6–8** to the desired α-alkoxyketones **1–3** has never been considered

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† Electronic supplementary information (ESI) available: Scanned copies of the ^{1}H and ^{13}C NMR spectra of α′-monoalkylated α-(m)ethoxyketones **1**, α,α′-dialkylated α-(m)ethoxyketones **2**, α-monoalkylated α-methoxyketones **3** and α,α,α′-trialkylated ketimine **10d**. See DOI: 10.1039/c0ob00662a

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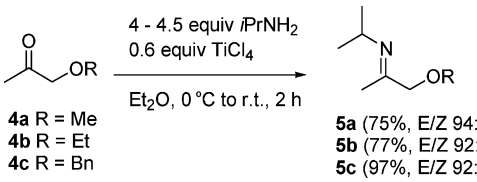
(Fig. 1). This alkylation strategy *via* 1-azaallylic anions as masked enolates,[40] is not only synthetically important to achieve a novel synthesis of α-alkoxyketones **1–3** but should also be interesting from a mechanistic point-of-view as it will provide experimental data leading to new important insights into the regioselectivity of the deprotonation and alkylation of unsymmetrical oxygenated ketimines.

Results and discussion

At the outset it was considered that the intermediate α-alkoxyketimines would be very unstable, and that the regioselective alkylation of α-alkoxyketimine **5** would not be as straightforward as in the case of α-chloroketimines.[41] The reason originates from the unclear steric, electronic and chelation effects of an alkoxy substituent at the α-position of an imino function combined with the known alkoxy deactivation effect in α-proton abstraction.[42] The regioselective deprotonation of α-alkoxyketones has already proven to be a complex research topic,[43] and the story for α-alkoxyketimines becomes even more complicated due to the additional presence of the *N*-substituent. It should be underlined that α-monoalkoxyketimines in *sensu stricto* such as substrates **5** have never been utilized in alkylation reactions. Only the fundamentally different α-alkylation of *O*-tetrahydropyranyl oxime ethers of α-hydroxyacetone derivatives, which involves substrate-specific base complexation and internal chelation steps due to the O-containing N-substituent,[44] the alkylation at the non-oxygenated carbon of the *N*-cyclohexylimine and *N*,*N*-dimethylhydrazone of the pyruvic aldehyde dimethyl acetal,[45] the α-alkylation of [(*S*)-1-(2,2-dimethyl-1,3-dioxan-5-ylideneamino)-2-methoxymethylpyrrolidine] to give 4-alkyl-2,2-dimethyl-1,3-dioxan-5-ones,[46] the conjugate additions of imine derivatives of α-alkoxy substituted cyclohexanones,[47] and organocatalyzed aldol,[48] Mannich,[49] and Michael additions[50] of α-methoxyacetone, hold some resemblance with the present alkylation procedure. The present methodology in this paper is far more the simplest approach.

N-(1-Methoxy-2-propylidene)isopropylamine **5a**, the corresponding ethoxy derivative **5b** and benzyloxy derivative **5c** were easily accessible in high purity by condensation of the corresponding α-alkoxyacetone derivative **4** with isopropylamine in the presence of a stoichiometric amount of titanium(IV) chloride (Scheme 1).[51] The noncommercial α-ethoxyacetone **4b** was synthesized in 60% yield by oxidation of 1-ethoxy-2-propanol with 3 equiv pyridinium chlorochromate (PCC) in dichloromethane for 40 h at room temperature. The α-alkoxyketimines **5** exist as an



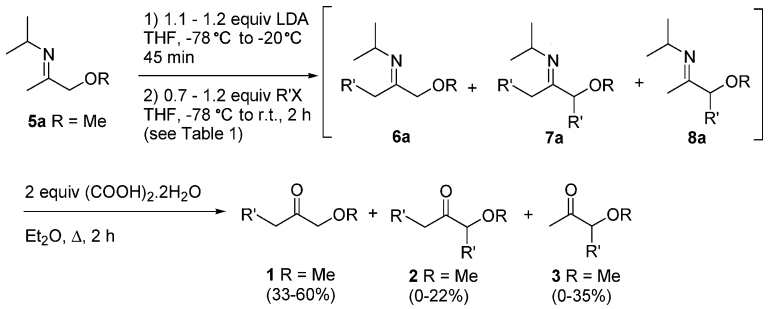
Scheme 1 Synthesis of α-alkoxyketimines **5** by condensation of the corresponding α-alkoxyacetone with isopropylamine.

equilibrium mixture of almost exclusively the *E*-isomer (≥ 92%) with respect to the imino function which was investigated by ASIS (Aromatic Solvent Induced Shift) measurements,[51a] and direct comparison of ^{1}H and ^{13}C NMR data of imines **5** with literature data of closely related α-phenoxyketimines.[52]

N-(1-Methoxy-2-propylidene)isopropylamine **5a** was readily deprotonated with 1.1–1.2 equiv of lithium diisopropylamide in tetrahydrofuran at −78 °C and subsequently treated with a slight excess of alkyl halides to afford the α′-monoalkylated α-methoxyketimines **6a** as the major compounds (Scheme 2, Table 1). A small difference in the ratio of the alkylated ketimines **6a–8a** was noted when their synthesis was performed at −78 °C, 0 °C or at room temperature, respectively, with a lower amount of the two minor compounds **7a** and **8a**, at the lowest temperature, and with a small increase in the final yield of the corresponding α-methoxy ketones **1–3**. The use of LiHMDS instead of LDA for the deprotonation of ketimine **5a** resulted in a disappointing conversion (32%) of **5a** to alkylated ketimines **6a–8a** and a lower regioselectivity (Table 1, entry 5).

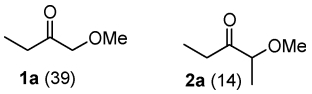
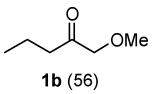
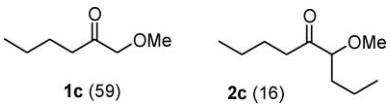
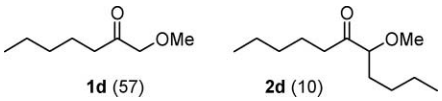
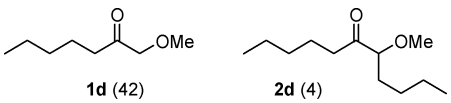
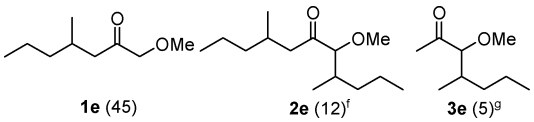
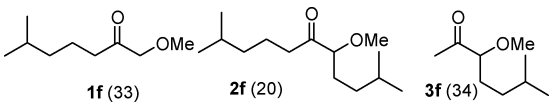
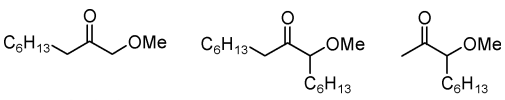
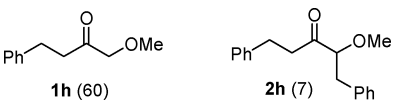
Together with compounds **6a**, the α,α′-dialkylated ketimines **7a** and in some cases the α-monoalkylated ketimines **8a** were present in the reaction mixture as minor compounds in a ratio depending on the alkyl halides used.

With the sterically smaller alkylating reagents (R′ = Me, Et, n-Pr, n-Bu), only α′-alkylation and α,α′-dialkylation products were observed. For example, when *N*-(1-methoxy-2-propylidene)isopropylamine **5a** was deprotonated with 1.1 equiv of LDA in THF at −78 °C for 45 min, during which the temperature reached −20 °C, and subsequently treated with 1.1 equiv *n*-BuBr at −20 °C for 2 h, during which the temperature reached room temperature, the α′-monoalkylated α-methoxyketimine **6a** was formed as the major compound (**6a**/**7a**/**8a**: 6/1/0, Table 1, entry 4). Treatment of the mixture of α-methoxyketimines **6a** and **7a** with 2 equiv of aqueous oxalic acid at reflux for 2 h, resulted in a mixture of the corresponding α-methoxyketones **1d** and **2d** (**1d**/**2d**/**3d**: 5/1/0). After flash chromatography the α′-monoalkylated α-methoxyketone **1d** and the α,α′-dialkylated



Scheme 2 Synthesis of α-methoxyketones **1–3** *via* α-, α′- and α,α′-(di)alkylation of α-methoxyketimine **5a**.

Table 1 Overview on the α-, α′- and α,α′-(di)alkylation of α-methoxyketimine **5a** with 0.7–1.2 equiv R′X

Entry	R′X	1) LDA 2) R′X (equiv)	Ratio **6a**/**7a**/**8a**[a]	Ratio 1/2/3[a]	Isolated products (%)[b]
1	MeI	1) 1.2[c] 2) 1.2[c]	3/1/0	3/1/0	 **1a** (39) **2a** (14)
2	EtBr	1) 1.1 2) 1.1	13/1/0	15/1/0	 **1b** (56)
3	*n*-PrBr	1) 1.2 2) 1.1	3/1/0	2.5/1/0	 **1c** (59) **2c** (16)
4	*n*-BuBr	1) 1.1 2) 1.1	6/1/0	5/1/0	 **1d** (57) **2d** (10)
5	*n*-BuBr	1) 1.1[d] 2) 1.1	2.2/1/0	—	—
6	*n*-BuBr	1) 1.1 2) 0.7	10/1/0	9/1/0[e]	 **1d** (42) **2d** (4)
7	2-Br-pentane	1) 1.2 2) 1.1	8.5/2.5/1	8/2.5/1	 **1e** (45) **2e** (12)[f] **3e** (5)[g]
8	*i*-PeBr	1) 1.2 2) 1.1	1.7/1/2	1.6/1/1.8	 **1f** (33) **2f** (20) **3f** (34)
9	1-Br-hexane	1) 1.2 2) 1.2	1.5/1/1.5	1.2/1/1.2	 **1g** (39) **2g** (22) **3g** (35)
10	$PhCH_2Br$	1) 1.1 2) 1.1	39/7/1	38/5/1	 **1h** (60) **2h** (7)

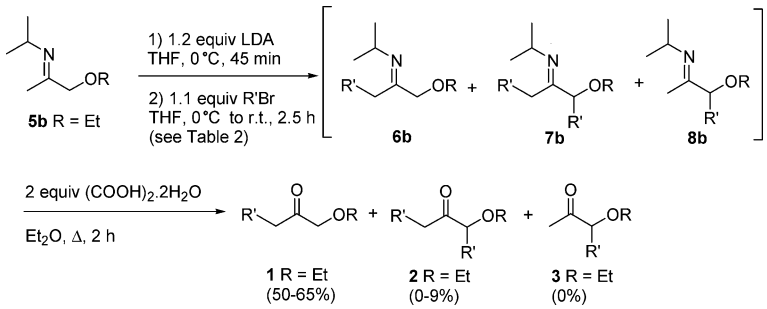
[a] Determined *via* GC-MS analysis of the crude reaction mixtures. [b] Yields of the compounds (90 → 99% purity determined *via* GC) after flash chromatography on silica gel. [c] This reaction was performed at a constant temperature of −78 °C. [d] LiHMDS was used instead of LDA resulting in a conversion of 32% of **5a** into alkylated ketimines **6a** and **7a**. [e] 68% conversion of ketimine **5a** to α-methoxyketones **1d** and **2d** was observed. [f] Compound **2e** could not be separated from compound **3e** (12%, **2e**/**3e** 8/1). [g] Compound **3e** could not be separated from compounds **1e** and **2e** (5%, **1e**/**2e**/**3e** 2/1/17).

α-methoxyketone **2d** were isolated in respectively 57% and 10% yield. The use of *n*-BuBr in a limiting amount (0.7 equiv) resulted even in a higher ratio of α′-monoalkylated α-methoxyketone **1d** over α,α′-dialkylated α-methoxyketone **2d** (**1d**/**2d** 9 : 1), but the isolated yields were lower due to an incomplete conversion of 68% of ketimine **5a** into α-methoxyketones **1d** and **2d** (Table 1, entry 6).

In contrast, when more sterically demanding alkylation reagents (R′ = C_5H_{11}, C_6H_{13}, $C_6H_4CH_2$) were used, the α-alkylation products were also formed in significant amounts. For example when 1-bromohexane was used as alkylating agent, α-methoxymethylketimine **8a** was obtained as the major compound, and the corresponding α-hexyl-α-methoxymethylketone **3g** was obtained in 35% overall yield after hydrolysis (Table 1, entry 9).

Comparable ratios were observed when isopentyl bromide was used as alkylating agent, resulting in the isolation of 3-methoxy-6-methyl-2-heptanone **3f** in 34% yield (Table 1, entry 8).

In all cases, the mixtures of α-methoxyketimines **6a**, **7a** and **8a** were smoothly hydrolyzed by aqueous oxalic acid in a biphasic system with diethyl ether, affording the corresponding α-methoxyketones **1**, **2** and **3** (Scheme 2, Table 1). The latter ketones could be easily separated by flash chromatography on silica gel, providing a synthetic method to various α-methoxyketones in



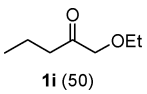
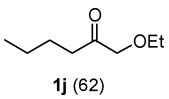
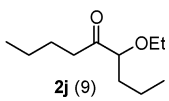
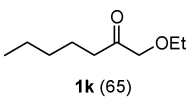
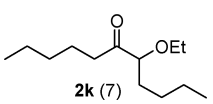
Scheme 3 Synthesis of α-ethoxyketones **1–3** *via* α-, α′- and α,α′-(di)alkylation of α-ethoxyketimine **5b**.

a preparative way. Noteworthy, the ratios of the isolated α-methoxyketones **1**, **2** and **3** sometimes differ from the ratios determined *via* GC-MS analysis of the crude reaction mixtures, probably due to the volatility of α-methoxyketones **1**, **2** and **3**.

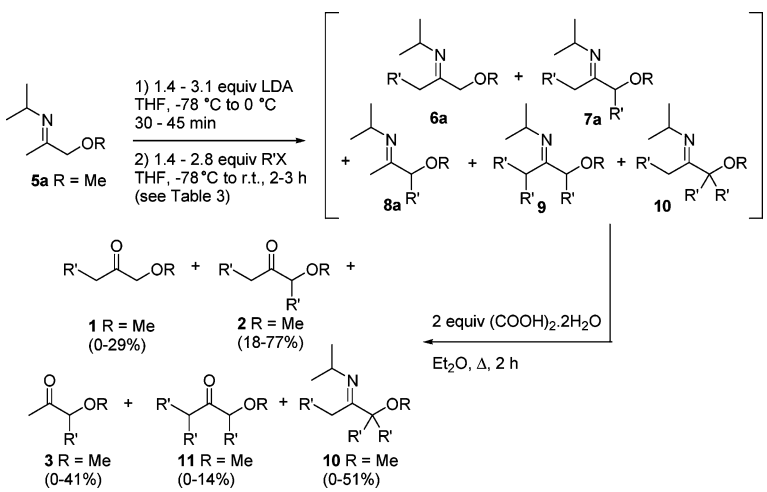
Although *N*-(1-methoxy-2-propylidene)isopropylamine **5a** is very unstable to moisture, the exclusive observation of α-methoxyketimines **6a**, **7a** and **8a** by GC-MS analysis provides evidence that there is no direct alkylation from α-methoxyacetone **4a**. In addition, when α-methoxyacetone **4a** was deprotonated with 1.1 equiv of lithium diisopropylamide in tetrahydrofuran at –78 °C and subsequently treated with a slight excess of *n*-BuBr, the formation of α-methoxyketones **1**, **2** and **3** could not be observed. Instead, a complex mixture of self-condensation products of **4a** was obtained.

Odorous α-methoxyketones **1a–c** have been prepared as analogues of acetoin (3-hydroxy-2-butanone), an important flavor compound, to study the aroma of sake,[24] while 1-methoxy-4-phenyl-2-butanone **1h** occurs as a volatile compound in green

Table 2 Overview on the α-, α′- and α,α′-(di)alkylation of α-ethoxyketimine **5b**

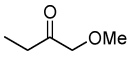
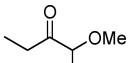
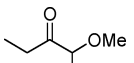
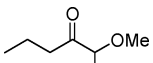
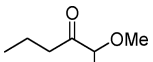
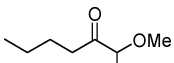
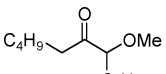
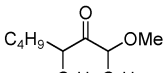
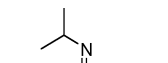
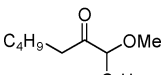
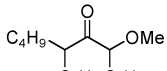
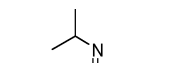
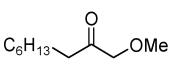
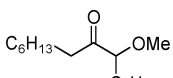
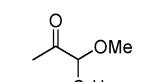
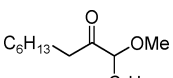
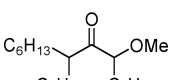
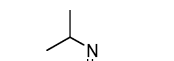
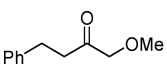
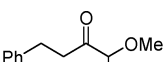
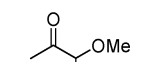
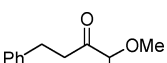
Entry	R′Br	Ratio **6b/7b/8b**[a]	Ratio **1/2/3**[a]	Isolated products (%)
1	EtBr	24/2/1	22/2/1	 **1i** (50)
2	*n*-PrBr	22/3/1	21/3/1	 **1j** (62)  **2j** (9)
3	*n*-BuBr	18/2/1	17/2/1	 **1k** (65)  **2k** (7)

[a] Determined *via* GC-MS analysis of the crude reaction mixtures.

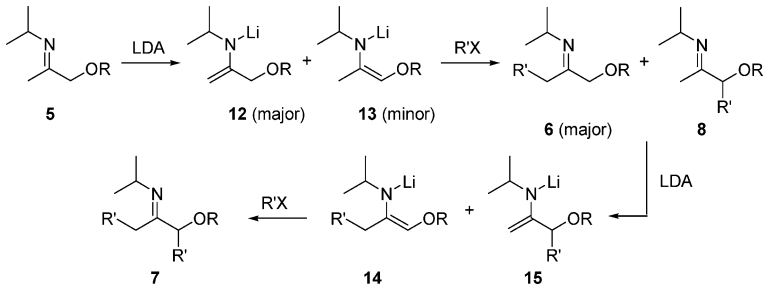


Scheme 4 Synthesis of α-methoxyketones **1–3** and/or α,α′,α′-trialkylated α-methoxyketones **11** *via* α-, α′- and α,α′-, α,α′,α′- and α,α,α′-(di)(tri)alkylation of α-methoxyketimine **5a**.

Table 3 Overview on the α-, α′- and α,α′-, α,α′,α′- and α,α,α′-(di)(tri)alkylation of α-methoxyketimine **5a** with 1.4–2.8 equiv R′X

Entry	R′X	1) LDA 2) R′X (equiv)	Ratio**1/2/3/11/10**[a]	Isolated products (%)[b]
1	MeI	1) 1.4[c] 2) 1.4[c]	1/1/0/0/0	 **1a** (29)  **2a** (27)
2	MeI	1) 2.2[d] 2) 2.2[d]	1/137/0/0/0	 **2a** (50)
3	EtBr	1) 1.9[d] 2) 1.7[d]	1/16/0/0/0	 **2b** (54)
4	EtBr	1) 2.4[e] 2) 2.2[e]	1/42/0/1/4	 **2b** (56)
5	*n*-PrBr	1) 2.4[e] 2) 2.2[e]	1/85/5/1/3	 **2c** (64)
6	*n*-BuBr	1) 2.4[d] 2) 2.4[d]	0/15/0/1/3.5	 **2d** (54)  **11d**[f]  **10d**[f]
7	*n*-BuBr	2) 2.8[e]	0/1/0/1.25/6	 **2d** (29)  **11d**[g]  **10d** (51)
8	1-bromo-hexane	1) 1.4[c] 2) 1.4[c]	1/2/1.5/0/0	 **1g** (23)  **2g** (26)  **3g** (19)
9	1-bromo-hexane	1) 2.2[d] 2) 2.2[d]	0/27/0/1/5.5	 **2g** (77)
10	1-bromo-hexane	1) 3.0[d] 2) 2.7[d]	0/1/0/4/15	 **11g**[h]  **10g**[h]
11	$PhCH_2Br$	1) 1.4[c] 2) 1.4[c]	1.5/1/1.9/0/0	 **1h** (29)  **2h** (18)  **3h** (41)
12	$PhCH_2Br$	1) 2.2[d] 2) 2.2[d]	1/8/1.1/0/0	 **2h** (67)

[a] Determined *via* GC-MS analysis of the crude reaction mixtures. [b] Yields of the compounds (90 → 99% purity *via* GC) after flash chromatography on silica gel. [c] Reaction conditions: 1) –78 °C, 45 min; 2) –78 °C, 2 h. [d] Reaction conditions: 1) –78 °C, 45 min; 2) –78 °C to rt, 3 h. [e] Reaction conditions: 1) 0 °C, 30 min; 2) 0 °C to rt, 3 h. [f] Compounds **10d** and **11d** could not be separated by flash chromatography (12%, **10d**/**11d** 7/3). [g] Compound **11d** could not be separated from compounds **2d** and **10d** (14%, **2d**/**10d**/**11d** 1/9/40). [h] Compounds **10g** and **11g** could not be separated by flash chromatography (76%, **10g**/**11g** 8/2).



Scheme 5 Proposed reaction pathway for the α-, α′- and α,α′-(di)alkylation of α-alkoxyketimines **5**.

heartwood of *Quercus pyrenaica* Wild. oak, which has potential use in barrels for aging wine.[53] 1-Methoxy-4-methyl-2-heptanone **1e** has been used in the synthesis of the aggregation pheromone lardolure.[4]

Noteworthy, when using the optimized conditions of the alkylation of *N*-(1-methoxy-2-propylidene)-isopropylamine **5a** (Scheme 2, Table 1), *i.e.* treating *N*-(1-ethoxy-2-propylidene)isopropylamine **5b** with 1.2 equiv of lithium diisopropylamide in tetrahydrofuran at −78 °C, followed by the addition of a slight excess of alkyl halides at −20 °C, no reaction was observed. However, deprotonation of *N*-(1-ethoxy-2-propylidene)isopropylamine **5b** with LDA at 0 °C in tetrahydrofuran, and subsequent alkylation with alkyl halides at 0 °C, afforded 1-ethoxy-2-ketimine **6b** predominantly after 2.5 h during which the temperature was risen to room temperature (Scheme 3, Table 2).

Via hydrolysis of the mixtures of α-ethoxyketimines **6b**, **7b** and **8b** by aqueous oxalic acid in a biphasic system with diethyl ether and separation by flash chromatography on silica gel, 1-ethoxy-2-alkanones **1i–k** were isolated as major compounds in similar or higher yields (50–65%) as compared to the corresponding α-methoxyketones **1b–d**, while α,α′-dialkylated α-ethoxyketones **2j** and **2k** were isolated as minor compounds. 1-Ethoxy-2-heptanone **1k** has been identified as a volatile compound of dry-cured ham,[22] and traditional balsamic vinegar.[23]

Unfortunately, all attempts to alkylate *N*-(1-benzyloxy-2-propylidene)isopropylamine **5c** by treatment with LDA and subsequent alkylation with alkyl halides, afforded mainly starting material, even when the reaction was performed at room temperature.

The double alkylation of methoxyketimine **5a** at the α- and α′-position towards the synthesis of dialkylated ketones **2** was also investigated. Therefore, *N*-(1-methoxy-2-propylidene)isopropylamine **5a** was treated with a larger excess of lithium diisopropylamide and subsequent treated with alkyl halides (Scheme 4, Table 3).

The formed ketimines **6a–9** were easily hydrolyzed by oxalic acid in a biphasic system with diethyl ether which afforded α′-monoalkylated α-methoxyketones **1**, α,α′-dialkylated α-methoxyketones **2**, α-monoalkylated α-methoxyketones **3** and/or α,α′,α′-trialkylated α-methoxyketones **11**. Surprisingly, the formed α,α,α′-trialkylated ketimines **10** did not hydrolyze by oxalic acid treatment (2 equiv oxalic acid, $Et_2O : H_2O$ 1 : 1, Δ, 2 h) and α,α,α′-trialkylated ketimine **10d** could be isolated in pure form by flash chromatography. Although unclear, probably, steric or solubility effects are responsible for the resistance of α,α,α′-trialkylated ketimines **10** to hydrolysis.

The ratio of the formed mono-, di- and trialkylated products **1–3**, **10**, **11** depends on the amount of base used and on the nature of the alkylating reagent. It is worth mentioning that 3-methoxy-4-heptanone **2b** has been used in flavor formulations with a pleasant raspberry aroma.[16]

The regioselectivity obtained in the lithiation and alkylation of unsymmetrical ketimines is determined by steric, electronic and chelation effects, which are case specific and depending on the nature of the base, imine substrate (*e.g. N*-substituent), solvent, temperature and additives.[54] Nevertheless, the experimentally observed selectivity in the α′-monoalkylation and α′,α-dialkylation of imines **5** corresponds with some general observations made in earlier studies leading to the reaction pathway as proposed in Scheme 5. Upon analyzing the experimental data reported above, it is clear that the *N*-isopropyl imines of α-alkoxyacetones **5** are predominantly kinetically α′-alkylated *via syn*-lithiation to **12** and subsequent *syn*-alkylation at the less-substituted carbon, that is the methyl group, to give ketimines **6** as major products (Scheme 5). This result is in accordance with the regioselectivity observed in the hindered lithium dialkylamide-mediated alkylations of the less-substituted methyl group of imines derived from unsymmetrical acyclic methylketones,[55] and opposite (!) to the regioselectivity observed in the LDA-mediated allylation and benzylation of O-tetrahydropyranyl oxime ethers of α-hydroxyacetone derivatives.[44]

α-Monoalkylation of the methoxy-substituted methylene group of **5a**, probably *via anti*-azaallylic anion **13**, to ketimine **8** becomes competitive only when 2-bromopentane, although to only a minor extent (Table 1, entry 7), and more importantly, isopentyl bromide (Table 1, entry 8), hexyl bromide (Table 1, entry 9 and Table 3, entry 8) or benzyl bromide (Table 3, entry 11) are used as alkylating reagents. These results indicate that the regioselectivity of the alkylation is influenced by steric effects of the electrophiles. α′-Alkylation is favored unless R′ becomes more sterically hindered (resulting in more α-alkylation) due to steric hindrance between the *N*-substituent and R′. The LDA-mediated alkylation of *syn*-alkylated ketimines **6** to the corresponding α,α′-dialkylated ketimines **7** occurs with complete regioselectivity since α′,α′-dialkylated compounds were not observed. This selective *anti*-lithiation of the methoxy-substituted methylene group to **14** is probably the result of the fact that the introduced α′-alkyl group retards deprotonation by lithium diisopropylamide at the α′-position of ketimines **6** which acts in concert with the steric interactions exerted by the branched *N*-isopropyl substituent with the hindered lithium diisopropylamide.[56] Dialkylated ketimines **7** can also result from *syn*-lithiation and alkylation of the less-substituted site of the α-alkylated ketimines **8**. The latter

α′-alkylation of α-alkylated ketimines **8** is probably significantly inhibited when R′ becomes too bulky and explains why the only α-monoalkylated ketones that could be isolated were ketones **3f–h**. In view of the strong oxophilicity of Li^+,[57] it is assumed that chelation between lithium and the oxygen of the alkoxy substituent in the intermediate 1-azaallylic anions **12–15** can be an important factor in the formation of the latter.[58]

Conclusion

In conclusion, α-methoxy- and α-ethoxyketones were synthesized by a simple two-step procedure. In a first step, deprotonation of *N*-(1-alkoxy-2-propylidene)isopropylamine, prepared from the corresponding α-alkoxyacetone derivative, and subsequent reaction of the corresponding 1-azaallylic anions with alkyl halides afforded α′-alkylated and α,α′-dialkylated ketimines. In a second step, hydrolysis of the imino function led to the desired substituted α-alkoxyketones. The ratio of α-, α′-, and α,α′-(di)alkylated compounds depended on the amount of base used and on the nature of the alkylating reagent. The used alkylation strategy led to important insights into the regioselectivity of the deprotonation and alkylation of α-alkoxyketimines and forms a convenient method for the synthesis of various α-alkoxyketones.

Experimental

General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere from sodium/benzophenone ketyl. All other chemicals were of commercial grade (Aldrich) and used without further purification. Petroleum ether refers to the 40–60 °C boiling fraction. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using the syringe-septum cap technique. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded in deuterated solvents with tetramethylsilane (TMS, $\delta = 0$ ppm) as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer (EI, 70 eV) by using GC-MS coupling or *via* a direct inlet system on a Agilent 1100 Series VS (ESI, 4000 V). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory. The purification of the reaction mixtures was performed by column chromatography with silica gel (particle size 0.035–0.070 mm, pore diameter *ca.* 6 nm). The purity (90–99%) of all isolated oily products was determined *via* GC.

Preparation of *N*-(1-methoxy-2-propylidene)isopropylamine (5a), *N*-(1-ethoxy-2-propylidene)isopropylamine (5b) and *N*-(1-benzyloxy-2-propylidene)isopropylamine (5c)

The preparation of the α-alkoxyimines **5a**, **5b** and **5c** was performed following an imination procedure described in the literature.[59]

***N*-(1-Methoxy-2-propylidene)isopropylamine (5a).** Yield = 75%. Bp 52 °C (33 mbar). ν_{max}/cm^{-1} 2968, 2820, 1660, 1108. δ_H(300 MHz, $CDCl_3$) *E*-isomer 1.13 (6 H, d, $J = 6.1$ Hz), 1.86 (3 H, s), 3.35 (3 H, s), 3.69 (1 H, septet, $J = 6.1$ Hz), 3.92 (2 H, s); *Z*-isomer 1.11 (6 H, d, $J = 6.1$ Hz), 2.04 (3 H, s), 3.36 (3 H, s), 3.69 (1 H, septet, $J = 6.1$ Hz), 4.04 (2 H, s). δ_C(75 MHz, $CDCl_3$) *E*-isomer 13.5, 23.0 (2C), 50.0, 57.7, 78.6, 163.8; *Z*-isomer 13.5, 23.4 (2C), 49.3, 58.4, 69.4, 164.8. *m*/*z* (EI, 70 eV): 129 (M^+, 4%), 84 (32), 43 (26), 42 (100).

***N*-(1-Ethoxy-2-propylidene)isopropylamine (5b).** Yield = 77%. Bp 65 °C (30 mbar). ν_{max}/cm^{-1} 2968, 2871, 1663, 1107. δ_H(300 MHz, $CDCl_3$) *E*-isomer 1.12 (6 H, d, $J = 6.1$ Hz), 1.23 (3 H, t, $J = 7.2$ Hz), 1.89 (3 H, s), 3.49 (2 H, q, $J = 7.2$ Hz), 3.69 (1 H, septet, $J = 6.1$ Hz), 3.96 (2 H, s); *Z*-isomer 1.08 (6 H, d, $J = 6.1$ Hz), 1.26 (3 H, t, $J = 7.2$ Hz), 2.05 (3 H, s), 3.56 (2 H, q, $J = 7.2$ Hz), 3.69 (1 H, septet, $J = 6.1$ Hz), 4.07 (2 H, s). δ_C(75 MHz, $CDCl_3$) *E*-isomer 14.1, 15.2, 23.4, 50.4, 65.9, 77.4, 165.1; *Z*-isomer 14.1, 15.1, 23.8, 49.6, 66.7, 77.4, 165.7. *m*/*z* (EI, 70 eV): 143 (M^+, < 2%), 84 (24), 43 (16), 42 (100).

***N*-(1-Benzyloxy-2-propylidene)isopropylamine (5c).** Yield = 97%. Bp 81 °C (0.1 mmHg). ν_{max}/cm^{-1} 2966, 1662, 1095, 736, 697. δ_H(300 MHz, $CDCl_3$) *E*-isomer 1.13 (6 H, d, $J = 6.1$ Hz), 1.88 (3 H, s), 3.68 (1 H, septet, $J = 6.1$ Hz), 4.01 (2 H, s), 4.51 (2 H, s), 7.23-7.39 (5 H, m); *Z*-isomer 1.13 (6 H, d, $J = 6.1$ Hz), 1.83 (3 H, s), 3.68 (1 H, septet, $J = 6.1$ Hz), 4.10 (2 H, s), 4.58 (2 H, s), 7.23–7.39 (5 H, m). δ_C(75 MHz, $CDCl_3$) *E*-isomer 14.3, 23.4 (2C), 50.5, 72.7, 77.7, 127.8, 128.0 (2C), 128.5 (2C), 138.1, 164.7; *Z*-isomer 14.7, 23.9 (2C), 49.7, 73.2, 77.7, 127.7, 128.0 (2C), 128.6 (2C), 137.7, 165.2. *m*/*z* (ES): 206 ([M + H]$^+$, 100%).

Synthesis of α′-monoalkylated α-(m)ethoxyketones 1, α,α′-dialkylated α-(m)ethoxyketones 2, α-monoalkylated α-methoxyketones 3, α,α,α′-trialkylated ketimines 10 and α,α′,α′-trialkylated α-methoxyketones 11

The preparation of 1-methoxy-2-pentanone **1b** is representative for all other preparations of α-alkoxyketones **1**, **2**, **3** and **11** and α-alkoxyimines **10**. The amount of base and alkyl halide used, the reaction temperature and the reaction time are given in Schemes 2–4 and Tables 1–3.

To a solution of freshly prepared LDA [1.1 equiv, 8.5 mmol; from 3.4 mL (8.5 mmol) 2.5 M butyllithium in hexane and 0.86 g (8.5 mmol) of diisopropylamine dissolved in tetrahydrofuran (10 mL)] was added dropwise *N*-(1-methoxy-2-propylidene)isopropylamine **5a** (1.0 g, 7.75 mmol), dissolved in THF (2 mL) at −78 °C under nitrogen atmosphere. After the addition was complete, the reaction mixture was stirred for 45 min, during which the temperature reached −20 °C. Subsequently, bromoethane (0.93 g, 8.5 mmol) was added dropwise at −20 °C, and the reaction mixture was stirred for 2 h during which the temperature reached room temperature. The reaction mixture was poured into 1 N (aq.) NaOH solution (20 mL) and extracted with diethyl ether (3 × 10 mL). After drying (K_2CO_3), the solvent was evaporated leaving a mixture of imines **6a** and **7** in a 13 : 1 ratio, respectively. The mixture of the two ketimines **6a** and **7** was used directly in the successive hydrolysis by oxalic acid (2.0 equiv, 1.4 g, 15.5 mmol) dissolved in H_2O (10 mL) in a biphasic system with diethyl ether (10 mL), at reflux for 2 h. After cooling of the reaction mixture, the organic phase was washed with saturated $NaHCO_3$ solution (20 mL) and dried ($MgSO_4$). After filtration and evaporation of the solvent, 0.90 g of a mixture of 1-methoxy-2-pentanone **1b** and 3-methoxy-4-heptanone **2b** (15 : 1 ratio, respectively) was obtained. Compounds **1b** and **2b** were

separated by flash chromatography (silica gel) with petroleum ether/diethyl ether (ratio 87 : 13) as eluent affording 0.50 g of pure 1-methoxy-2-pentanone **1b** (yield = 56%).

1-Methoxy-2-butanone (1a). Yield = 39%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 85/15, $R_f = 0.16$). δ_H(300 MHz, $CDCl_3$) 1.09 (3 H, t, J = 7.2 Hz), 2.47 (2 H, q, J = 7.2 Hz), 3.42 (3 H, s), 4.03 (2 H, s). All spectroscopic data were in good agreement with reported data.[13]

1-Methoxy-2-pentanone (1b). Yield = 56%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 87/13, R_f = 0.17). δ_H(300 MHz, $CDCl_3$) 0.94 (3 H, t, J = 7.2 Hz), 1.63 (2 H, sextet, J = 7.2 Hz), 2.42 (2 H, t, J = 7.2 Hz), 3.42 (3 H, s), 4.02 (2 H, s). All spectroscopic data were in good agreement with reported data.[1]

1-Methoxy-2-hexanone (1c). Yield = 59%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 90/10, R_f = 0.23). δ_H(300 MHz, $CDCl_3$) 0.91 (3 H, t, J = 7.2 Hz), 1.33 (2 H, sextet, J = 7.2 Hz), 1.58 (2 H, quintet, J = 7.2 Hz), 2.44 (2 H, t, J = 7.6 Hz), 3.42 (3 H, s), 4.02 (2 H, s). All spectroscopic data were in good agreement with reported data.[11]

1-Methoxy-2-heptanone (1d). Yield = 57%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 90/10, R_f = 0.16). ν_{max}/cm^{-1} 2821, 1718. δ_H(300 MHz, $CDCl_3$) 0.89 (3 H, t, J = 7.2 Hz), 1.19–1.39 (4 H, m), 1.60 (2 H, quintet, J = 7.2 Hz), 2.43 (2 H, t, J = 7.2 Hz), 3.42 (3 H, s), 4.02 (2 H, s). δ_C(75 MHz, $CDCl_3$) δ 13.9, 22.4, 23.1, 31.4, 38.8, 59.3, 77.6, 208.7. m/z (EI, 70 eV): 144 (M^+, 5%), 99 (76), 71 (47), 45 (40), 43 (100).

1-Methoxy-4-methyl-2-heptanone (1e). Yield = 45%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 87/13, R_f = 0.32). δ_H(300 MHz, $CDCl_3$) 0.89 (3 H, t, J = 6.6 Hz), 0.90 (3 H, d, J = 6.6 Hz), 1.06–1.43 (4 H, m), 2.05 (1 H, m), 2.24 (1 H, d × d, J = 15.7, 8.0 Hz), 2.40 (1 H, d × d, J = 16.0, 6.1 Hz), 3.42 (3 H, s), 4.00 (2 H, s). All spectroscopic data were in good agreement with reported data.[4]

1-Methoxy-6-methyl-2-heptanone (1f). Yield = 33%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 85/15, R_f = 0.28). ν_{max}/cm^{-1} 2954, 1719, 1124. δ_H(300 MHz, $CDCl_3$) 0.88 (6 H, d, J = 6.6 Hz), 1.12–1.28 (2 H, m), 1.48–1.65 (3 H, m), 2.41 (2 H, t, J = 7.2 Hz), 3.42 (3 H, s), 4.02 (2 H, s). δ_C(75 MHz, $CDCl_3$) δ 21.2, 22.5 (2C), 27.8, 38.5, 39.0, 59.3, 77.6, 208.8. m/z (ES): 173 ([M + H]$^+$, 100%).

1-Methoxy-2-nonanone (1g). Yield = 39%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 85/15, R_f = 0.12). δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, J = 7.2 Hz), 1.08–1.43 (8 H, m), 1.59 (2 H, quintet, J = 7.2 Hz), 2.43 (2 H, t, J = 7.2 Hz), 3.42 (3 H, s), 4.01 (2 H, s). All spectroscopic data were in good agreement with reported data.[35]

1-Methoxy-4-phenyl-2-butanone (1h). Yield = 60%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 80/20, R_f = 0.17). δ_H(300 MHz, $CDCl_3$) 2.68–2.81 (2 H, m), 2.84–2.97 (2 H, m), 3.37 (3 H, s), 3.96 (2 H, s), 7.12–7.32 (5 H, m). All spectroscopic data were in good agreement with reported data.[36]

1-Ethoxy-2-pentanone (1i). Yield = 50%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 80/20, R_f = 0.08). ν_{max}/cm^{-1} 2965, 1720, 1118. δ_H(300 MHz, $CDCl_3$) 0.91 (3 H, t, J = 7.2 Hz), 1.26 (3 H, t, J = 7.2 Hz), 1.63 (2 H, sextet, J = 7.2 Hz), 2.43 (2 H, t, J = 7.2 Hz), 3.55 (2 H, q, J = 7.2 Hz), 4.05 (2 H, s). δ_C(75 MHz, $CDCl_3$) 13.8, 15.1, 16.9, 40.8, 67.2, 75.9, 209.2. m/z (ES): 131 ([M + H]$^+$, 100%).

1-Ethoxy-2-hexanone (1j). Yield = 62%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 92/8, R_f = 0.20). ν_{max}/cm^{-1} 2960, 1719, 1118. δ_H(300 MHz, $CDCl_3$) 0.91 (3 H, t, J = 7.2 Hz), 1.25 (3 H, t, J = 7.2 Hz), 1.33 (2 H, sextet, J = 7.2 Hz), 1.58 (2 H, pentet, J = 7.2 Hz), 2.45 (2 H, t, J = 7.2 Hz), 3.55 (2 H, q, J = 7.2 Hz), 4.05 (2 H, s). δ_C(75 MHz, $CDCl_3$) 13.9, 15.1, 22.4, 25.5, 38.6, 67.1, 75.9, 209.4. m/z (ES): 145 ([M + H]$^+$, 100%).

1-Ethoxy-2-heptanone (1k). Yield = 65%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 92/8, R_f = 0.21). ν_{max}/cm^{-1} 2931, 1718, 1119. δ_H(300 MHz, $CDCl_3$) 0.89 (3 H, t, J = 7.2 Hz), 1.21–1.39 (4 H, m), 1.26 (3 H, t, J = 7.2 Hz), 1.60 (2 H, pentet, J = 7.2 Hz), 2.44 (2 H, t, J = 7.2 Hz), 3.55 (2 H, q, J = 7.2 Hz), 4.05 (2 H, s). δ_C(75 MHz, $CDCl_3$) 14.0, 15.1, 22.5, 23.1, 31.5, 38.9, 67.2, 75.9, 209.4. m/z (ES): 159 ([M + H]$^+$, 100%).

2-Methoxy-3-pentanone (2a). Yield = 50%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 92/8, R_f = 0.21). ν_{max}/cm^{-1} 2924, 1720, 1119. δ_H(300 MHz, $CDCl_3$) 1.07 (3 H, t, J = 7.2 Hz), 1.30 (3 H, d, J = 7.2 Hz), 2.56 (2 H, q, J = 7.2 Hz), 3.36 (3 H, s), 3.75 (1 H, q, J = 7.2 Hz). δ_C(75 MHz, $CDCl_3$) 7.4, 17.3, 30.5, 57.6, 82.9, 207.2. m/z (EI, 70 eV): 116 (M^+, 29%), 91 (16), 70 (27), 57 (27), 40 (100).

3-Methoxy-4-heptanone (2b). Yield = 56%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 90/10, R_f = 0.26). δ_H(300 MHz, $CDCl_3$) 0.93 (6 H, t, J = 7.2 Hz), 1.54–1.72 (4 H, m), 2.48 (2 H, t, J = 7.2 Hz), 3.35 (3 H, s), 3.53 (1 H, t, J = 6.6 Hz). All spectroscopic data were in good agreement with reported data.[16,32b]

4-Methoxy-5-nonanone (2c). Yield = 64%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 90/10, R_f = 0.70). δ_H(300 MHz, $CDCl_3$) 0.92 (6 H, t, J = 7.2 Hz), 1.21–1.46 (4 H, m), 1.49–1.64 (4 H, m), 2.50 (2 H, t, J = 7.2 Hz), 3.34 (3 H, s), 3.58 (1 H, t, J = 6.6 Hz). All spectroscopic data were in good agreement with reported data.[37]

5-Methoxy-6-undecanone (2d). Yield = 54%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 90/10, R_f = 0.36). ν_{max}/cm^{-1} 2930, 2872, 1716, 1103. δ_H(300 MHz, $CDCl_3$) 0.90 (6 H, t, J = 7.2 Hz), 1.19–1.43 (8 H, m), 1.49–1.70 (4 H, m), 2.49 (2 H, t, J = 7.2 Hz), 3.34 (3 H, s), 3.56 (1 H, t, J = 6.3 Hz). δ_C(75 MHz, $CDCl_3$) 13.9 (2C), 22.5, 22.6, 22.9, 27.3, 31.5, 31.7, 37.4, 58.1, 87.4, 213.4. m/z (EI, 70 eV): 200 (M^+, 1%), 101 (100), 45 (56), 43 (18), 41 (21).

2,10-Dimethyl-5-methoxy-6-undecanone (2f). Yield = 20%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 85/15, R_f = 0.66). ν_{max}/cm^{-1} 2954, 1716, 1104. δ_H(300 MHz, $CDCl_3$) 0.89 (12 H, d, J = 6.6 Hz), 1.10–1.34 (4 H, m), 1.46–1.67 (6 H, m), 2.48 (2 H, t, J = 7.2 Hz), 3.34 (3 H, s), 3.55 (1 H, t, J = 6.6 Hz). δ_C(75 MHz, $CDCl_3$) δ 21.1, 22.4, 22.5 (4C), 27.9, 30.0, 34.2, 37.7, 38.6, 58.1, 87.6, 213.4. m/z (ES): 257 ([M + H]$^+$, 100%).

1-Methoxy-1-hexyl-2-nonanone (2g). Yield = 77%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 85/15,

$R_f = 0.38$). ν_{max}/cm^{-1} 2926, 2856, 1716, 1105. δ_H(300 MHz, $CDCl_3$) 0.88 (6 H, t, $J = 7.2$ Hz), 1.00–1.47 (16 H, m), 1.48–1.71 (4 H, m), 2.49 (2 H, t, $J = 7.2$ Hz), 3.34 (3 H, s), 3.57 (1 H, t, $J = 6.3$ Hz). δ_C(75 MHz, $CDCl_3$) 14.0 (2C), 22.5, 22.6, 23.2, 25.1, 29.1 (2C), 29.3, 31.6, 31.7, 32.0, 37.5, 58.1, 87.4, 213.3. *m/z* (EI, 70 eV): 256 (M^+, <1%), 129 (100), 97 (83), 55 (93), 45 (43), 43 (24), 41 (21), 40 (33).

2-Methoxy-1,5-diphenyl-3-pentanone (2h). Yield = 67%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 92/8, $R_f = 0.22$). ν_{max}/cm^{-1} 2929, 1714, 1100. δ_H(300 MHz, $CDCl_3$) 2.61–2.95 (6 H, m), 3.24 (3 H, s), 3.80 (1 H, d × d, $J = 7.2$, 5.0 Hz), 7.07–7.33 (10 H, m). δ_C(75 MHz, $CDCl_3$) 29.2, 38.2, 40.4, 58.5, 88.1, 126.2, 126.8, 128.6 (4C), 129.5 (4C), 137.1, 141.2, 211.8. *m/z* (ES): 267 ([M − H]$^+$, 100%).

4-Ethoxy-5-nonanone (2j). Yield = 9%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 92/8, $R_f = 0.51$). ν_{max}/cm^{-1} 2873, 1715, 1105. δ_H(300 MHz, $CDCl_3$) 0.91 (3 H, t, $J = 7.2$ Hz), 0.92 (3 H, t, $J = 7.2$ Hz), 1.23 (3 H, t, $J = 7.2$ Hz), 1.26–1.67 (8 H, m), 2.49 (1H, d × t, $J = 17.6$, 7.4 Hz), 2.53 (1H, d × t, $J = 17.6$, 7.6 Hz), 3.41 (1H, d × q, $J = 9.4$, 7.0 Hz), 3.49 (1H, d × q, $J = 9.4$, 7.0 Hz), 3.65 (1 H, d × d, $J = 7.7$, 5.0 Hz). δ_C(75 MHz, $CDCl_3$) 13.9, 14.0, 15.4, 18.8, 22.5, 25.4, 34.5, 37.1, 66.2, 85.7, 214.3. *m/z* (ES): 187 ([M + H]$^+$, 100%).

5-Ethoxy-6-undecanone (2k). Yield = 7%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 92/8, $R_f = 0.55$). ν_{max}/cm^{-1} 2930, 2871, 1715, 1107. δ_H(300 MHz, $CDCl_3$) 0.90 (6 H, t, $J = 7.2$ Hz), 1.23 (3 H, t, $J = 7.2$ Hz), 1.24–1.46 (8 H, m), 1.52-1.65 (4 H, m), 2.49 (1H, d × t, $J = 17.6$, 7.3 Hz), 2.52 (1H, d × t, $J = 17.6$, 7.6 Hz), 3.42 (1H, d × q, $J = 9.1$, 7.0 Hz), 3.49 (1H, d × q, $J = 9.4$, 7.1 Hz), 3.63 (1 H, d × d, $J = 7.2$, 6.1 Hz). δ_C(75 MHz, $CDCl_3$) 14.0 (2C), 15.4, 22.6 (2C), 23.0, 27.6, 31.6, 32.1, 37.3, 66.1, 85.9, 214.3. *m/z* (ES): 215 ([M + H]$^+$, 100%).

3-Methoxy-6-methyl-2-heptanone (3f). Yield = 34%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 85/15, $R_f = 0.45$). ν_{max}/cm^{-1} 2955, 1713, 1103. δ_H(300 MHz, $CDCl_3$) 0.81 (6 H, d, $J = 7.2$ Hz), 1.09–1.28 (2 H, m), 1.39-1.61 (3 H, m), 2.08 (3 H, s), 3.28 (3 H, s), 3.46 (1 H, t, $J = 6.6$ Hz). δ_C(75 MHz, $CDCl_3$) 22.3, 22.4, 25.0, 27.9, 29.7, 34.0, 58.0, 87.7, 211.4. *m/z* (ES): 173 ([M + H]$^+$, 100%).

3-Methoxy-2-nonanone (3g). Yield = 35%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 85/15, $R_f = 0.19$). ν_{max}/cm^{-1} 2928, 2859, 1715, 1103. δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, $J = 6.6$ Hz), 1.12–1.47 (8 H, m), 1.51–1.71 (2 H, m), 2.16 (3 H, s), 3.36 (3 H, s), 3.55 (1 H, t, $J = 6.6$ Hz). δ_C(75 MHz, $CDCl_3$) 14.0, 22.6, 25.0 (2C), 29.1, 31.7, 31.9, 58.0, 87.6, 211.3. *m/z* (EI, 70 eV): 172 (M^+, <1%), 97 (41), 55 (63), 45 (37), 43 (31), 40 (100).

3-Methoxy-4-phenyl-2-butanone (3h). Yield = 41%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 80/20, $R_f = 0.24$). ν_{max}/cm^{-1} 2931, 1713, 1104. δ_H(300 MHz, $CDCl_3$) 2.09 (3 H, s), 2.82–3.01 (2 H, m), 3.30 (3 H, s), 3.79 (1 H, d × d, $J = 7.4$, 5.0 Hz), 7.11–7.33 (5 H, m). δ_C(75 MHz, $CDCl_3$) 26.0, 38.2, 58.4, 88.3, 126.8, 128.5 (2C), 129.4 (2C), 137.1, 211.0. *m/z* (EI, 70 eV): 179 (M^+, <1%), 133 (41), 105 (98), 91 (100), 45 (31).

***N*-(2-Butyl-2-methoxy-1-pentylhexylidene)isopropylamine (10d).** Yield = 51%. Flash chromatography on silica gel, (petroleum ether/diethyl ether: 97/3, $R_f = 0.64$). ν_{max}/cm^{-1} 2930, 1655, 1459, 1084. δ_H(300 MHz, $CDCl_3$) 0.81–0.97 (9 H, m), 1.09 (6 H, d, $J = 6.1$ Hz), 1.11–1.16 (3 H, m), 1.21–1.45 (11 H, m), 1.52–1.77 (4 H, m), 2.15–2.27 (2 H, m), 3.05 (3 H, s), 3.76 (1 H, septet, $J = 6.1$ Hz). δ_C(75 MHz, $CDCl_3$) 14.0, 14.2 (2C), 22.3, 23.2 (2C), 24.0 (2C), 25.5 (2C), 27.2, 27.4, 32.7, 33.1 (2C), 49.6, 50.3, 84.2, 171.2. *m/z* (ES): 298 ([M + H]$^+$, 100%).

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