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Synthesis and olfactory properties of unnatural derivatives of lilac aldehydes

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ABSTRACT

Lilac aldehydes are considered as principal olfactory molecules of lilac flowers. We have designed, prepared and evaluated two sets of their unnatural racemic analogues as pure diastereomers. While the synthesis of *gem*-dimethyl homologues starts from geranyl acetate, the preparation of methylene derivatives commences from linalyl acetate. The key Lewis and/or Brønsted acid catalysed cyclisation furnishes easily separable *cis*-/*trans*-tetrahydrofuranyl esters as common advanced intermediates. The subsequent functional group transformations lead to target aldehydes, alcohols, nitriles and olefins. Unlike the homologues possessing similar herbal scents, methylene derivatives exhibit woody and/or flowery odours. In the latter case, the sensory evaluation suggests the importance of relative stereochemistry and/or type of functional group on the odour character of respective compounds.

1. Introduction

Lilac aldehydes[1] **1** (Fig. 1) are naturally occurring monocyclic tetrahydrofuranyl terpenes considered as principal olfactory molecules of lilac flowers (*Syringa vulgaris* L., Oleaceae). Their biogenetic formation from isopentenyl diphosphate and dimethylallyl diphosphate was proposed and investigated.[2] Various diastereomers of lilac aldehydes were also found in mixtures of volatile components from numerous plant species including flowers of kiwifruit[3a] (*Actinidia arguta*), White Campion[3b] (*Silene latifolia*), and Lesser Butterfly orchid (*Platanthera bifolia*).[3c] Thus not surprisingly, lilac aldehydes are of special interest for pollinators. It is known that these monoterpenes are highly attractive to the (nocturnal) moth species[4] as well as butterflies.[5] Despite the unique olfactory characteristics of lilac, until now there is no commercially available lilac flower oil, although many attempts have been made to produce satisfactory lilac concentrates.[6] Because no natural lilac flower oil is being produced so far, synthetically prepared lilac aldehydes are used in perfumery. Interestingly, the major naturally occurring (5′*S*)-stereoisomers **1a**–**d** have the odour threshold lower by 1–2 orders of magnitude in comparison to lilac aldehydes **1e**–**h** with (5′*R*)-absolute configuration[7] (Fig. 1).

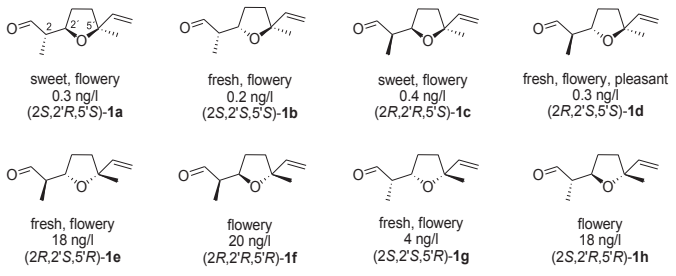

Fig. 1. Structures of lilac aldehydes **1a**–**h** with their odour thresholds.

There are numerous syntheses of racemic[3a,4b,8] and enantiomerically pure[7,9] lilac aldehydes **1** known to date. To the best of our knowledge, however, there is no comprehensive study available that would investigate the importance of respective substituents on the genuine flowery odour of lilac aldehydes. Therefore, we have designed and prepared two racemic sets of unnatural derivatives of lilac aldehydes: while the first one comprises diastereomerically pure *gem*-dimethyl homologues **2**–**7** (Fig. 2), the second one consists of methylene analogues **8**–**10** (Fig. 3). All of these novel derivatives feature a lower degree of asymmetry by having only two instead of naturally three stereogenic centres, either due to the incorporation of additional methyl group at the C-2 position or, conversely, removal of the existing one. In the first case, such a homologation also prevents otherwise feasible enolisation of

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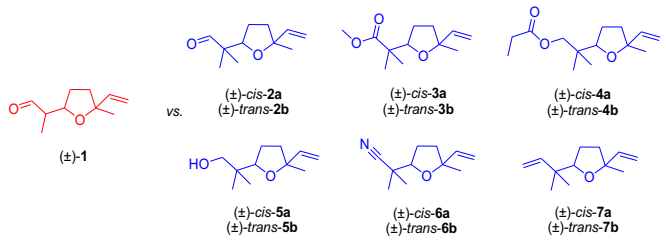


Fig. 2. Homologated unnatural derivatives **2**–**7** of lilac aldehydes **1**.

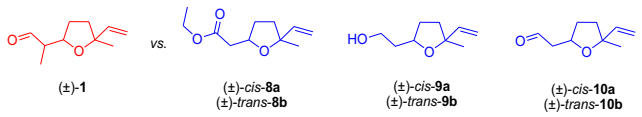


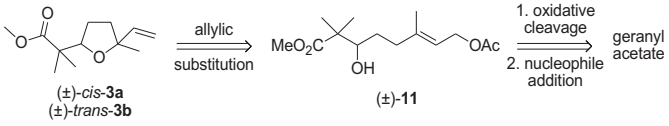
Fig. 3. Demethylated unnatural derivatives **8**–**10** of lilac aldehydes **1**.

a carbonyl group that might, however, negatively influence the stability of the fragrance molecules. Moreover, we have also replaced the original aldehydic group of **1** for esters **3**, **4** and **8**, alcohols **5** and **9**, nitrile **6** and olefin **7** (Figs. 2 and 3).

2. Results and discussion

2.1. Retrosynthetic analysis of homologues 2–7

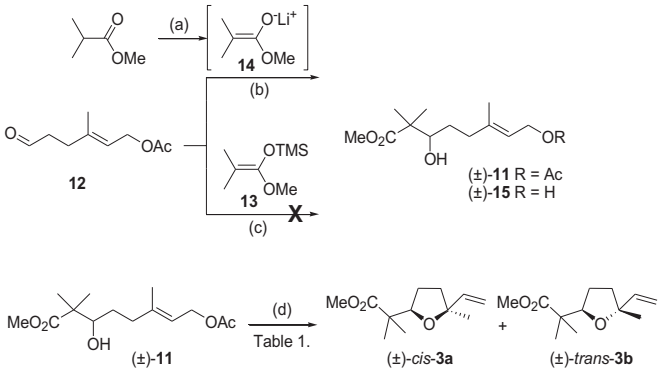
The retrosynthetic analysis of racemic C-2 homologues **2**–**7** relies on diastereomerically pure methylesters (±)-**3** as common synthetic intermediates. These key building blocks are, in turn, readily accessible from commercially available geranyl acetate via initial epoxidation[10]–cleavage[11]–addition[12] sequence followed by cyclisative allylic *O*-substitution[13] of hydroxydiester (±)-**11** (Scheme 1).



Scheme 1. Retrosynthetic analysis of key intermediates (±)-**3**.

2.2. Synthesis of homologues 2–7

The synthesis of racemic homologues **2**–**7** starts with the known[14] aldehyde **12** prepared by a two-step protocol[15] from geranyl acetate. The subsequent nucleophilic addition[12] of in situ prepared ketene acetal required considerable experimentation. While the silylated enol ether **13** did not furnish the desired product at all (zero conversion of **12** even at rt), the low temperature addition of lithium enolate **14** led to the hydroxydiester (±)-**11**. However, the (isolated) yield of the adduct was strongly dependent on the amount of nucleophile. While the use of 1.5 M equiv of **14** led to the incomplete (75%) conversion of aldehyde **12**, addition of 1.85 M equiv of ketene acetal to **12** furnished mainly the dihydroxyester (±)-**15** as a product of in situ deacetylation[16] of initially formed adduct (±)-**11**. Thus, the optimised protocol involved addition of 1.65 M excess of lithium enolate **14** to aldehyde **12** at −85 °C to obtain the desired hydroxydiester (±)-**11** in 65% yield after FLC (Scheme 2). This compound was subsequently used for the key cyclisative allylic substitution (Table 1). Among Lewis acids tested, bismuth(III) triflate[17] afforded the highest combined yield of desired methylesters (±)-**3** (85%). Analogously, the Brønsted-type triflic acid[18] also furnished tetrahydrofuranyl esters (±)-**3** in high yield. However, the diastereoselectivity in both cases was poor (cis/trans ~ 1:1.3). Nevertheless, racemic diastereomers were (partially) separable by careful flash chromatography on silica gel. The relative configurations of (±)-*cis*-**3a** and (±)-*trans*-**3b** were assigned on the basis of 1D NOESY spectra (Fig. 4).



Scheme 2. Reagents and conditions: (a) *n*-BuLi, *i*-Pr_2NH, methyl-2-methylpropionate, THF, 0 °C, 2 h; (b) **14** (1.65 equiv), THF, −85 °C, 2 h, FLC (65% (±)-**11**); (c) **13** (2 equiv), DCM, −80 °C to rt, 7 d (0% conversion of **12**); (d) Lewis/Brønsted acid (0.015–0.1 equiv), DCM (see Table 1).

Subsequently, pure diastereomers (±)-*cis*-**3a** and (±)-*trans*-**3b** were transformed to racemic targets **2**, **4**–**7**. Thus, hydride reduction[19] of separated methylesters (±)-**3** furnished the homologues of lilac alcohols (±)-*cis*-**5a** and (±)-*trans*-**5b** in practically quantitative yield (Scheme 3). Next, alcohols (±)-*cis*-**5a** and (±)-*trans*-**5b** were: (a) oxidised[20] to homologues of lilac aldehydes (±)-*cis*-**2a** and (±)-*trans*-**2b**; (b) acylated[21] with propanoic anhydride to esters (±)-*cis*-**4a** and (±)-*trans*-**4b** in high yields. Finally, the aldehydes (±)-*cis*-**2a** and (±)-*trans*-**2b** were transformed to: (a) nitriles (±)-*cis*-**6a** and (±)-*trans*-**6b** via intermediary imines using iodine in aq ammonia at sub-zero temperature;[22] (b) dienes (±)-*cis*-**7a** and (±)-*trans*-**7b** via Wittig reaction[23] in good to high yields (Scheme 3).

2.3. Retrosynthetic analysis of analogues 8–10

Having prepared the set of homologated derivatives **2**–**7** of lilac aldehydes **1**, we turned our attention to the synthesis of racemic C-2 demethylated analogues **8**–**10**. Their retrosynthetic analysis relies on diastereomerically pure ethylesters (±)-**8** as common synthetic intermediates. These key building blocks are, in turn, readily accessible from commercially available linalyl acetate via initial epoxidation[10]–oxidative cleavage[11]–Wittig olefination[24] sequence followed by Zemplen deacetylation of diester (±)-**16** with concomitant in situ base catalysed cyclisative Michael addition[25] (Scheme 4).

2.4. Synthesis of analogues 8–10

The synthesis of racemic analogues **8**–**10** starts with the known[26] aldehyde (±)-**17** prepared by two-step protocol[27] from linalyl acetate. The Wittig olefination[24] of (±)-**17** with commercially available phosphorane **18** furnished exclusively (*E*)-configured unsaturated diester (±)-**16** in moderate yield. Subsequently, its allylic acetate was deacetylated with sodium ethoxide to provide a corresponding allylic alcohol. This intermediate underwent in situ intramolecular 1,4-conjugate addition[28] to the unsaturated ester moiety to furnish desired tetrahydrofurans (±)-**8**, however, in moderate combined yield and non-stereoselectively (Scheme 5).[29] Nevertheless, racemic diastereomers were (partially) separable by careful flash chromatography on silica gel. The relative configurations of (±)-*cis*-**8a** and (±)-*trans*-**8b** were assigned on the basis of 1D NOESY spectra (Fig. 5).