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Efficient one-step synthesis of trialkylsubstituted 2(5*H*)-furanones utilizing direct Ti-crossed aldol condensation and its application to the straightforward synthesis of (*R*)-mintlactone and (*R*)-menthofuran†

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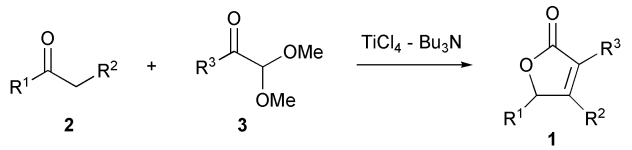
$TiCl_4$–Bu_3N-mediated condensation of ketones with α,α-dimethoxyketones afforded trialkylsubstituted 2(5*H*)-furanones in a one-pot manner, wherein aldol addition and furanone formation occurred sequentially; its application to straightforward synthesis of (*R*)-mintlactone and (*R*)-menthofuran, two representative natural mint perfumes, is demonstrated.

2(5*H*)-Furanones (α,β-butenolides) comprise an important heterocycle incorporated in natural products and serve as useful synthetic building blocks for lactones and furans.[1] There are many methods available for their synthesis, however, the majority of these are limited to the production of mono or dialkylsubstituted 2(5*H*)-furanones.[1] Previously, one of the authors (Y. T.) reported the synthesis of trialkylsubstituted 2(5*H*)-furanones **1** using enol silyl ethers and α,α-dimethoxyketones, however, three tedious steps were required: (i) preparation of enol silyl ethers, (ii) isolation of multi-functional labile aldol adducts, and (iii) use of dry HCl gas for furanone formation.[2] Recently, we developed direct and powerful Ti-aldol addition reactions using ketones and simple esters, demonstrating an ability to form C–C bonds which rivals or surpasses hitherto reported aldol additions.[3] We report here the $TiCl_4$–Bu_3N-mediated method for the preparation of trialkylsubstituted 2(5*H*)-furanones **1** (Scheme 1), and its application to the one-step total synthesis of (*R*)-mintlactone (**7**), and two-step synthesis of (*R*)-menthofuran (**11**), two representative commercial flavoring materials in natural American peppermint oil, isolated from *Menta piperita*.[4]



Scheme 1

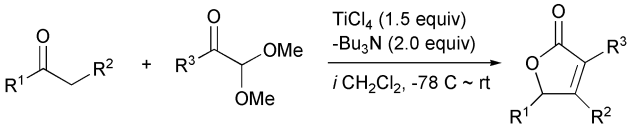
The present reaction was guided by the reaction of propiophenone (**2a**) with 1,1-dimethoxyacetone (**3a**) and the desired trialkylsubstituted compound was obtained in 77% yield under optimized conditions (Table 1). Several other analogs were successfully prepared in moderate to good yield.‡

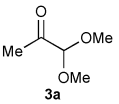
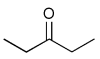
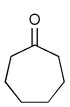
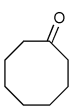
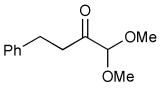
This synthetic method has several advantages over the previously reported one:[2] (i) one-step synthesis; (ii) does not require the preparation of enol silyl ethers (direct use of starting ketones) and the isolation of labile aldol intermediates; and (iii) higher total yields. The proposed mechanism (reaction sequence) is illustrated in Scheme 2: Initial Ti-mediated direct aldol addition gives aldol adduct **4**; subsequent formation of dihydrofuran **5**, followed by elimination of $Ti(OH)Cl_3$ gives 1-methoxyfurane **5′**, and final isomerization leads to 2(5*H*)-furanones **1**.

To demonstrate the present protocol, we performed a simple and straightforward synthesis of both natural (*R*)-mintlactone (**7**)[5] and (*R*)-menthofuran (**11**)[6] (Scheme 3). Because of their interesting structure and usefulness, these compounds have been challenging synthetic targets. Our present method seems to be the simplest of the reported methods, because of the one-step synthesis of **7** and the easy transformation of **7** to **11**, using commercially available substrates and reactants [3-(*R*)-methylcyclohexanone **6** and 1,1-dimethoxyacetone (**3a**)]. Thus, (*R*)-mintlactone (**7**) was successfully obtained in 52% yield and **7** was converted into **11** by the reported LAH–*i*-PrOH-reduction[5a] in 80% yield.§

C–C bond formation occurred regioselectively at the 6-position of **6** *anti* to 3-methyl (regioisomers **9** and **10** were not detected). In addition, furanone formation was stereoselective, since stereoisomeric (*R*)-isomintlactone (**8**) was a very minor product (< 10%). Computer-assisted conformation analysis supports the difference in the energy gap: **7** is 5.46 kcal mol^{-1}

Table 1 Preparation of trialkylsubstituted 2-(5*H*)-furanones **1** from ketones **2** and α,α-dimethoxyketones **3** using the $TiCl_4$–Bu_3N system



Ketone **2**	α,α-Dimethoxyketone **3**	Yield (%)
 **2a**	 **3a**	77
		33
		55
		64
		76
		65
		55

† Electronic supplementary information (ESI) available: calculated structures of **7** and **8**. See http://www.rsc.org/suppdata/cc/b2/b208077j/

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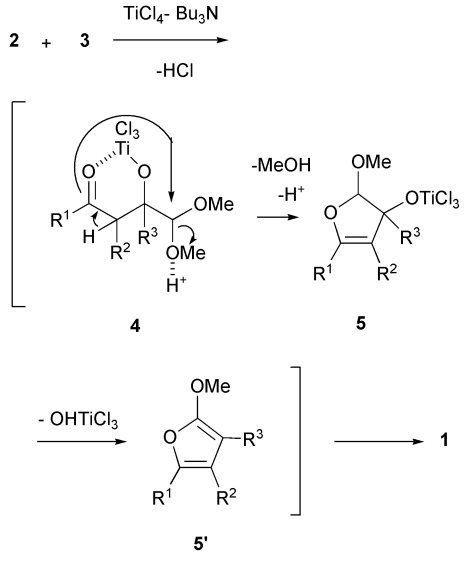

Scheme 2

more stable than **8** in the most stable conformation of each compound, probably because **7** has a chair-form cyclohexane, whereas **8** has a twisted boat-form cyclohexane [calculation was performed using SPARTAN '02 Windows (Wavefunction, Inc. Irvine, CA), Hartree-Fock, 6-31G*] (see ESI†).

In conclusion, we achieved a general synthetic method for trialkylsubstituted 2(5*H*)-furanones **1** utilizing direct Ti-aldol condensation and applied it to efficient total syntheses of (*R*)-mintlactone (**7**) and (*R*)-menthofuran (**11**).

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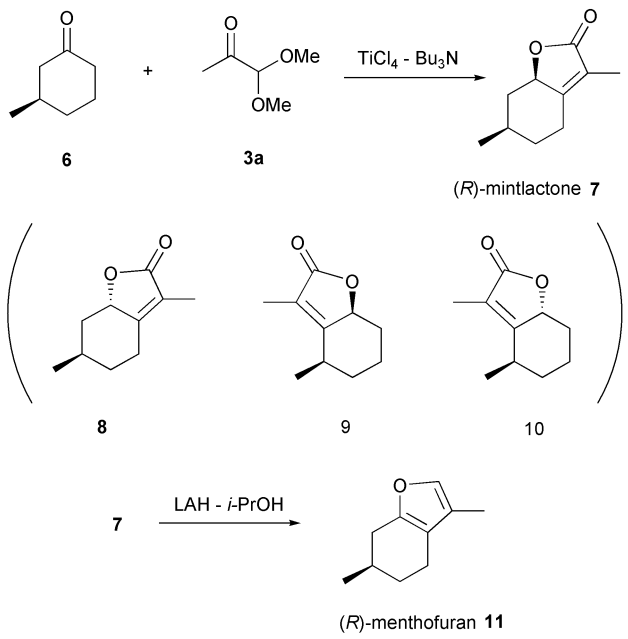

Scheme 3

Notes and references

‡ *Typical procedure* exemplified by the synthesis of (*R*)-mintlactone (**7**): $TiCl_4$ (1.0 M solution in CH_2Cl_2; 1.5 cm³, 1.5 mmol) and Bu_3N (371 mg, 2.00 mmol) in dry CH_2Cl_2 (0.5 cm³) were successively added to a stirred solution of 3-(*R*)-methylcyclohexanone (112 mg, 1.00 mmol) in dry CH_2Cl_2 (2.0 cm³) at −78 °C under an argon atmosphere, followed by stirring for 0.5 h. To the reaction mixture, 1,1-dimetoxy-2-propanone (236 mg, 2.00 mmol) in dry CH_2Cl_2 (0.5 cm³) was added. Then, the mixture was allowed to warm to room temp. and was stirred for 14 h. Water was added to the mixture, which was extracted with diethyl ether (5 cm³ × 3). The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained oil was purified by column chromatography on silica gel (hexane–ether = 5:1) to give the desired product (87 mg, 52%) as colorless oil. $[\alpha]_D^{20}$ −51.4 (*c*, 0.842, EtOH) [lit.[4a] $[\alpha]_D^{20}$ −51.8 (*c*, 10, EtOH)]. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.61 (1H, br dd, *J* 11.3, 6.1 Hz), 2.79 (1H, ddd, *J* 13.5, 4.5, 2 Hz), 2.41 (1H, dddd, *J* 12, 6.1, 2.5, 2.5 Hz), 2.20 (1H, br ddd, *J* 13.5, 13.5, 5.5 Hz), 1.93 (1H, ddddd, *J* 13, 5.5, 2.5, 2.5, 2 Hz), 1.79 (3H, t, *J* 1.6 Hz), 1.70 (1H, m), 1.00 (3H, d, *J* 6.6 Hz), 1.10–0.90 (2H, m). ^{13}C NMR (100 MHz; $CDCl_3$): δ 174.86, 162.32, 119.56, 79.92, 41.94, 34.51, 29.75, 25.44, 21.24, 8.20. IR (neat) 2954, 2927, 2862, 1741, 1683, 1445, 1371, 1325, 1296, 1265, 1243, 1094, 1072, 1030, 997, 857, 765, 735 cm^{-1}.

§ (*R*)-Menthofuran (**11**). colorless oil. $[\alpha]_D^{20}$ +95.3 (*c*, 0.842, EtOH) [lit.[4b] $[\alpha]_D^{25}$ +95.6 (*c*, 10, EtOH)]. Other spectroscopic data matched those reported in the literature.[4a,6]

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