# A Versatile Synthesis of Butenolides

Total Synthesis of (+/-)-Mintlactone

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Summary: The butenolide monoterpenes, mintlactone and isomintlactone, have been synthesized by a new method for the preparation of butenolides from α,β-unsaturated esters by deconjugation, epoxidation and rearrangement.

The α,β-butenolide (2(5H)-furanone) functionality is widely distributed in nature and has attracted a great deal of synthetic interest.[1] We have now developed a new approach to the synthesis of butenolides and have applied it to the total synthesis of three naturally occurring butenolides, terelactone (**1**) and the monoterpenes mintlactone (**2**) and isomintlactone (**3**).[2] Butenolide **1** has been isolated from the essential oils of a variety of plants,[3] while **2** and **3** are found in peppermint oil, and **2** is also present in other Mentha species, including spearmint oil.[4]

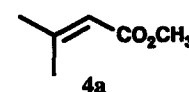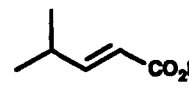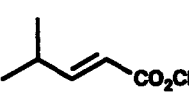| 1 | 2 | 3 |
| terelactone | (-)-mintlactone | (+)-isomintlactone |
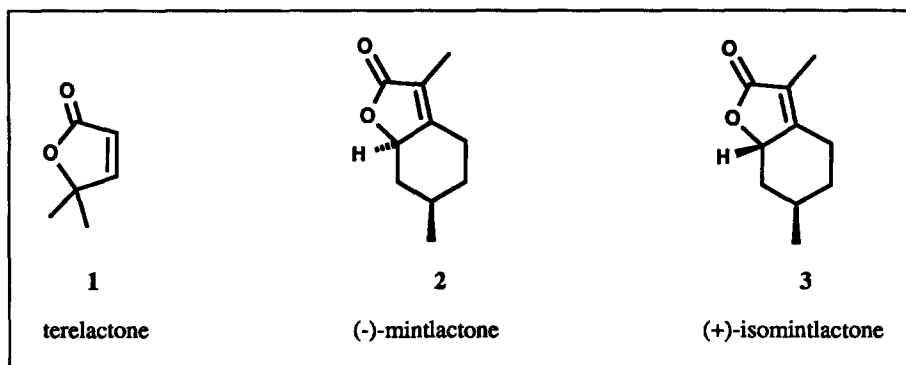
The key sequence involves the preparation of the butenolide moiety from an α,β-unsaturated ester (**4**) by the following series of reactions: deconjugation[5] (LDA, HMPA, THF; AcOH or MeI) (with or with out concomitant methylation at the α-position) to a β,γ-unsaturated ester (**5**), epoxidation (MCPBA, CHCl₃), and rearrangement of the resulting β,γ-epoxy ester (**6**) to an α,β-butenolide (**7**) with loss of alcohol (R₁OH). The last step may be carried out under either acidic or basic conditions,[6] and representative examples are shown in the table.

The yields are generally acceptable, and the conversion of the β,γ-unsaturated ester (**5**) to the butenolide (**7**) may be carried out without isolation of the epoxy ester (**6**). For example, treatment of unsaturated ester **5c** with MCPBA in chloroform followed by addition of trifluoroacetic acid (TFA) gave butenolide **7c** in 72% yield.[6] The overall yield of **7c** in two steps from α,β-unsaturated ester **4c** was thus 43%.

4 **5** **6** **7**
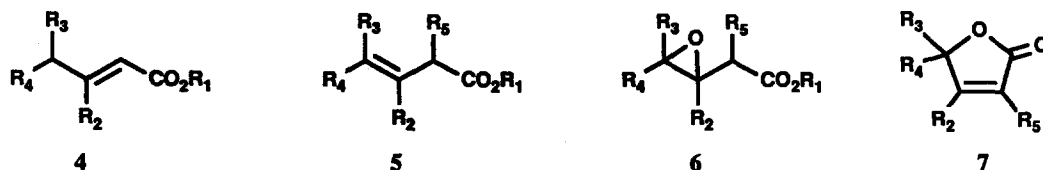
a) $R_1, R_2 = Me$; $R_3, R_4, R_5 = H$; b) $R_1 = Me$; $R_2 = H$; $R_3, R_4 = Me$; $R_5 = H$; c) $R_1 = Me$; $R_2 = H$; $R_3, R_4, R_5 = Me$

| Entry	Conjugated Ester or Acid	Deconjugated Ester (% yield)	Epoxy Ester (% yield)	Butenolide (% yield)	Method[a]
1	**4a** (CO_2CH_3)	**5a** (62)	**6a** (55)	**11**[b] (26)	A
2	(CO_2H)	**5b** (70)[c]	**6b** (73)	**7b** (75)	B
3	**4c** (CO_2CH_3)	**5c** (60)	**6c** (76)	**7c** (70)	B
4	**8**	**9** (80)	**10** (70)	**2/3** (68)	A

[a]For **6 → 7**. A = LDA, THF, HMPA, reflux; B = CF_3CO_2H, $CHCl_3$.
[b]Hydroxy ester (no butenolide formed).
[c]Over two steps: deconjugation (KOH, H_2O, reflux) and esterification.

**4c** $\xrightarrow[\text{2) MeI}]{\text{1) LDA}}$ **5c** $\xrightarrow[\text{2) TFA}]{\text{1) MCPBA}}$ **7c**
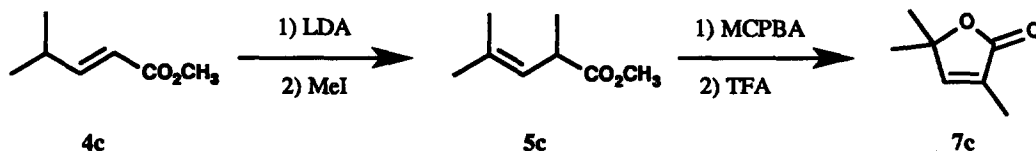
The synthesis of mintlactone and isomintlactone started with Emmons-Wadsworth olefination of 4-methyl-cyclohexanone ([MeO]$_2$POCH$_2$CO$_2$Me, NaH, benzene, 60-65 °C), which afforded α,β-unsaturated ester **8** in 65% yield. Alkylative deconjugation to **9** (mixture of diastereomers) and epoxidation to **10** (also a mixture) proceeded without difficulty, and the key rearrangement step, performed under basic conditions, gave a 9:1 mixture of (±)-mintlactone (**2**) and (±)-isomintlactone (**3**), from which (±)-mintlactone could be isolated pure in 68% yield.[9] Rearrangement of epoxy ester **10** under acidic conditions gave a complex mixture of products.
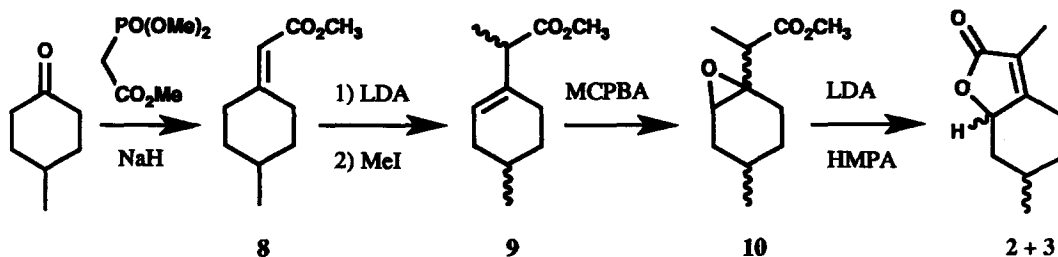
A limitation of this method became evident when attempts to prepare the β-methyl substituted butenolide 7a were not successful due to the failure of the last step. In this case acid-catalyzed rearrangement of epoxy ester 6a gave a mixture in which 7a was not present, and treatment of 6a with LDA in HMPA/THF gave only a relatively low yield of hydroxy ester 11, the remainder of the product mixture being non-volatile. Interestingly, 11 has been converted to 7a by other methods.[10]
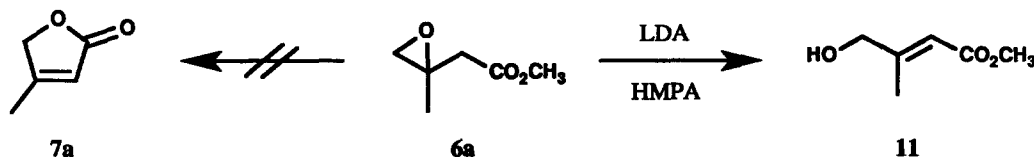
Although the formation of hydroxy ester 11 was not the desired result, it did offer some insight into the mechanism of the base-catalyzed rearrangement. In fact, if HMPA and heat are avoided in those reactions which would otherwise produce butenolides, only the corresponding (*trans*) hydroxy esters are isolated. For example, epoxy ester 6b gave a 63% yield of hydroxy ester 12[11] on treatment with LDA in THF at -78 °C, and no butenolide could be detected. As with 11, 12 has previously been transformed into the corresponding butenolide, terelactone (1 = 7b), by more cumbersome sequences of reactions.[7] It would thus appear that HMPA is essential to facilitate the isomerization of the intermediate E-α,β-unsaturated ester-alkoxide to its geometric isomer by intramolecular alkoxide addition to the α,β-unsaturated ester moiety.[12] Cyclization of the Z-α,β-unsaturated ester-alkoxide to the corresponding butenolide is presumably quite rapid.
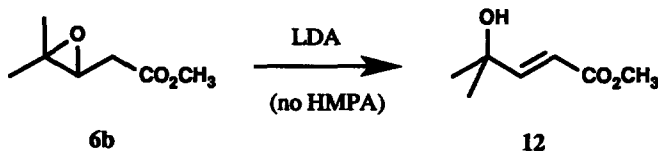
Failure of the acid-catalyzed rearrangement in the cases of epoxy esters 6a and 10 may be attributed to regio-selective ring-opening of the epoxide in a sense opposite to the other examples, driven by carbocation stability. It is particularly noteworthy that, in contrast to acid-catalysis, base-induced rearrangement of 10 to mintlactone and isomintlactone was successful, demonstrating that the two conditions are complementary to each other to some extent and that both are therefore useful.

References and Notes

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2. Portions of this work were presented at the Tenth International Congress of Heterocyclic Chemistry by one of us (BMR) August 13, 1985 at Waterloo, Ontario, Canada.

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4. Takahashi, K.; Someya, T.; Muraki, S.; Yoshida, T. *Agric. Biol. Chem.* **1980**, *44*, 1535-1543. Comparison of the ^{1}H NMR spectra shown in this paper with those of our synthetic 2 and 3 served to confirm their identities.

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6. Representative procedures:

   Method A: To 3.0 mmol of LDA and 5.6 mmol of HMPA in THF under argon at -78 °C was added 2.5 mmol of epoxy ester 10 in THF. The mixture was warmed gradually to room temperature and finally heated at reflux for 18 h. Aqueous work-up gave a 9:1 mixture of 2 and 3.
   Method B: To 0.5 mL of CF_3CO_2H in $CHCl_3$ was added 2.0 mmol of epoxy ester 6b, and the solution was stirred for 6 h. Aqueous work-up afforded terelactone[7] (1 = 7b).
   Without isolation of the epoxy ester: To 0.045 mol of MCPBA in $CHCl_3$ was added 0.030 mol of unsaturated ester 5c in $CHCl_3$. The mixture was stirred for 2 h and then filtered. To the filtrate was added 5 mL of CF_3CO_2H, and the solution was stirred for 6 h. Aqueous work-up gave butenolide 7c, mp 53-55 °C (lit[8] mp 56-57 °C).

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11. Previous synthesis: Tanikaga, R.; Nozaki, Y.; Tamura, T.; Kaji, A. *Synthesis* **1983**, 134-135.

12. See also: Armstrong, R. J.; Harris, F. L.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 1002-1006; Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087-3114.