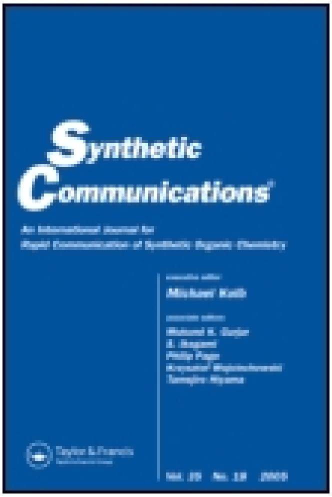

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A FACILE SYNTHESIS OF (±)-MINTLACTONE

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Abstract: (±)-Mintlactone has been synthesized by applying a novel effective synthetic sequence. 4-Methylcyclohexanone was subjected to acetoxylation with $Pb(OAc)_4$. Hydrolysis followed by reaction with 2-chloropropionyl chloride,then treatment with triethyl phosphite and, finally, Horner-Emmons-type intramolecular cyclization afforded (±)-Mintlactone.

The essential oil of *Mentha piperita* L. (peppermint oil), one of the most important commercial flavoring materials, is produced in many countrie. Its chemical composition has been investigated, more than 300 components having been reported[1]. Among the minor constituents, (±)-Mintlactone (3,6-dimethyl-5,6,7,7a-tetrahydro-2(4H) benzofuranone) was isolated from a sample of American peppermint oil[2].After its first description as a natural product, stereoselective and nonselective syntheses of (±)-Mintlactone have been

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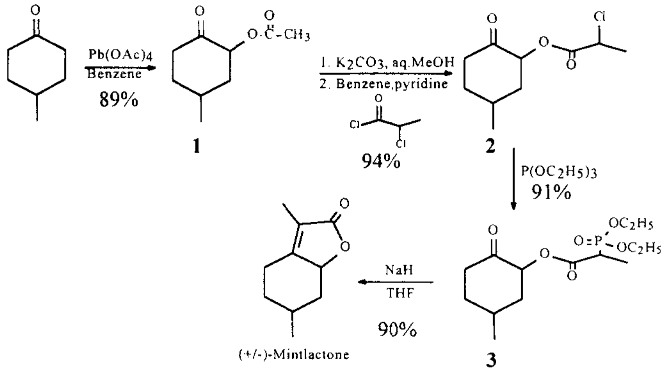
reported[3-8]. In all these syntheses, yields varied in the range 33% to 80% and the syntheses are multistep.

In this article, we report a new and short way for the synthesis of (±)-Mintlactone with high chemical yield as shown in scheme 1. In the synthetic strategy, in connection with our preceding works[9], we oxidized 4-methylcyclohexanone as starting compound by a mild oxidizing agent lead (IV) acetate to introduce oxygen function at the 2-position. Hydrolysis of the ester followed by re-esterification with 2-chloropropionyl chloride proceeded smoothly. We also applied the $Mn(OAc)_3$ oxidation of 4-methylcyclohex-2-en-1-one in the presence of 2-chloropropionic acid followed by the reduction with H_2 catalyzed by Pd(C) to afford directly 4-methyl-2-(2-chloropropionyloxy)cyclohexanone[10]. This was quite a short way compared with the above procedure,but the yield was lower. Subsequent application of the Arbuzov reaction in the presence of triethyl phosphite followed by Horner-Emmons type intramolecular cyclization reaction afforded (±)-Mintlactone.



Scheme 1

Experimental Section:

^{1}H-NMR and ^{13}C-NMR spectra were determined in $CDCl_3$ as solvent using Bruker Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane. IR spectra were obtained from a Perkin Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Elemental Analyses were performed on a LECO 932.

2-Acetoxy-4-methylcyclohexanone **(1)**

4-Methylcyclohexanone (1.12 g, 40 mmol) and $Pb(OAc)_4$ (3.95 g, 40 mmol) in benzene (15 ml) were heated at 80°C until no test for the oxidant was obtained. The mixture was washed with H_2O (4x20 ml), and dried over $MgSO_4$. The residue was purified by flash column chromatography using 4:1 n-hexane/ethyl acetate as the eluent to give the product **1**[11]. (89% yield); ^{1}H-NMR ($CDCl_3$): δ (ppm): 0.75-0.98 (m, 3H, CH_3), 2.10 (s, 3H, CH_3), 1.60-2.45 (m, 6H, CH_2), 5.15 (dd, 1H, CHO); IR (neat) ν (max): 1734 cm^{-1}; Anal. calc. For $C_9H_{14}O_3$: C, 63.51; H, 8.29; Found: C, 63.47; H, 8.25.

2-Hydroxy-4-methylcyclohexanone

K_2CO_3 (1.6 g, 11.7 mmol) was dissolved in MeOH by adding a small amount of water. Compound **1** (2.0 g, 11.7 mmol) was added slowly to the K_2CO_3 solution and stirred at room temperature for 15 minutes. The mixture was hydrolyzed with 1N HCl and then extracted with ethyl acetate (3x25 ml). The residue was purified by flash column chromatography using 4:1 n-hexane/ethyl acetate as the eluent to give 2-hydroxy-4-methylcyclohexanone[11]. (98% yield); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.78-1.10 (m, 3H, CH_3), 1.60-2.25 (m, 6H, CH_2), 3.60 (broad, 1H, OH), 5.10 (dd, 1H, CHO); IR (neat) ν (max): 3469, 1715 cm^{-1}; Anal. calc. for $C_7H_{12}O_2$: C, 65.32; H, 9.40; Found: C, 65.34; H, 9.37.

2-(2-Chloropropionyloxy)-4-methylcyclohexanone **(2)**

2-Hydroxy-4-methylcyclohexanone (1.00 g, 7.8 mmol) dissolved in benzene (15 ml) was mixed with dry pyridine (0.6 g, 8.3 mmol). The resultant mixture was stirred in an ice bath for 20 min. Then to this mixture, 2-chloropropionyl chloride (1.38 g, 11.1 mmol) was added dropwise under argon atmosphere. The mixture was kept in an ice bath for 1h and for 2h at room temperature. The mixture was extracted with water (2x20 ml). The residue was purified by flash column chromatography using 4:1 n-hexane/ethyl acetate as the eluent. (94% yield); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.65 (d, 3H,CH_3), 1.80 (d, 3H, $CHClCH_3$), 1.85-2.45 (m, 6H, CH_2), 4.45 (q, 1H, CHCl), 5.10 (dd, 1H, CHO); IR (neat) ν (max): 1734 cm^{-1}; Anal. calc. for $C_{10}H_{15}ClO_3$: C, 54.92; H, 6.91; Found: C, 54.95; H, 6.87.

2-(2-Diethoxyphosphoryl)propionyloxy-4-methylcyclohexanone **(3)**

A mixture of compound **2** (0.57 g, 2.6 mmol) and triethyl phosphite (1.73 g, 10 mmol) was refluxed under argon atmosphere for 3 h. The excess of triethyl phosphite was distilled off *in vacuo*. This gave **3** in 91% yield; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.7-0.95 (m, 6H, $\underline{CH_3}$-CH_2), 1.18 (d, 3H, CH_3), 1.40-2.30 (m, 6H, CH_2), 3.55-4.05 (m, 4H, CH_3-$\underline{CH_2}$), 4.30-4.45 (m, 1H, C$\underline{H}$P), 4.86-5.15 (dd, 1H, C$\underline{H}$O); Anal. calc. for $C_{14}H_{25}O_6P$: C, 52.49; H, 7.87; Found: C, 52.53; H, 7.81.

(±)-Mintlactone

To a solution of compound **3** (0.70 g, 2.2 mmol) in THF (30 ml) was added NaH (0.096 g, 4.0 mmol) under argon atmosphere. The resulting mixture was refluxed for 4 h. Then the reaction mixture was allowed to cool to room temperature and quenched with water. The resulting mixture was extracted with ethyl acetate (3x25 ml). The organic solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography using 4:1 n-hexane/ethyl acetate as the eluent. (90% yield); IR and NMR data wereidentical with those of the authentic sample[2,8]; Anal. calc. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49; Found: C, 72.31; H, 8.43.

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References

1. Lawrence, B. M.; Hogg, J. W. and Terhune, S. J. *Flavor Industry* **1972**, 467.
2. Takahashi, K.; Someya, T.; Muraki, S. and Yoshida, T. *Agric. Biol. Chem.* **1980**, *44*, 1535.
3. Takeda, A.; Tsuboi, S. and Shimozuma, K. *J. Org. Chem.* **1980**, *45*, 1517.
4. Cory, R. M.; Ritchie, B. M. and Shrier, A. M. *Tetrahedron Lett.* **1990**, 6789.
5. Carda, M. and Marco, J. A. *Tetrahedron Lett.* **1991**, *32*, 5191.
6. Chavan, S. P.; Zubaidha, P. K. and Ayyangar, N. R. *Tetrahedron Lett.* **1992**, *33*, 4605.
7. Shishido, K.; Irie, O. and Shibuya, M. *Tetrahedron Lett.* **1992**, *33*, 4589.

8. Chavan, S. P.; Zubaidha, P. K. and Dhondge, V. D. *Tetrahedron* **1993**, 49, 6429.

9. Tanyeli, C.; Demir, A. S. and Dikici, E. *Tetrahedron:Asymmetry* **1996**, 7, 2399.

10. Demir, A. S.; Akgün, H.; Tanyeli, C.; Sayraç, Tugmac, S. and Watt, D. S. *Synthesis* **1991**, 719.

11. May, G. M. and Pinhey, J. T. *Aust. J. Chem.* **1982**, *35*, 1859.

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