Facile Synthesis of β-Hydroxy-γ-Varelolactone *via* the Ring Opening Reaction of β-Trichloromethyl-β-Propiolactone with Ester Enolates

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(Received April 25, 1997; CL-970310)

The reaction of enantiomerically pure (*S*)-β-trichloromethyl-β-propiolactone with the enolate derived from *t*-butyl acetate gave δ-hydroxy-β-ketoester in good yield. Subsequent *syn*-selective reduction of ketone and cyclization gave β-hydroxy-γ-varelolactones in good yield in enantiomerically pure form. The β-hydroxy-γ-varelolactones thus obtained are excellent precursors for the synthesis of compactin and mevinolin derivatives of potent inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMG CoA reductase).

Among β-hydroxy-γ-varelolactones, compactin **4a** and mevinolin **4b** families constitute attractive derivatives due to their highly therapeutic index in humans in connection with the inhibition abilities of HMG CoA reductase,[1] and several reviews for their preparations and biomedical properties have appeared.[2] For the preparation of β-hydroxy-γ-varelolactones, their lactone moieties, several approaches have been reported. One of the most convenient approaches involves the construction of 5-substituted 3,5-dihydroxypentanoic acid.[3] To this end malic acid derivatives have been used due to ready availability and handlings.[3] On the other hand, regioselective ring cleavage of β-methyl-β-propiolactones with organocopper reagents has been reported to provide a convenient synthesis of carbon homologated carboxylic acids by the oxygen-alkyl bond fission in an S_N2 fashion.[4] In contrast to this observation, we have found that β-trichloromethyl-β-propiolactone reacted with nucleophiles to give oxygen-acyl bond fission products, and those arising from oxygen-alkyl bond fission were not obtained. This may be due to the strong electron-withdrawing ability and steric bulk of the trichloromethyl group. As one of these examples, we have recently reported that (*R*)-β-trichloromethyl-β-propiolactone serves as a convenient chiral C-4 unit for the acylation of aromatic compounds,[5] and the acylated product **2** was successfully converted into a precursor of enalapril **3**, an angiotensin converting enzyme (ACE) inhibitor in enantiomerically pure form. In this communication we would like to report that the reaction of enantiomerically pure (*S*)-β-trichloromethyl-β-propiolactone (*S*)-**1**[6] with the enolate derived from *t*-butyl acetate gave δ-hydroxy-β-ketoester, an oxygen-acyl bond fission product, in good yield, and the subsequent stereoselective *syn*-reduction and ring closure lead to the formation of β-hydroxy-γ-varelolactone, a lactone part of compactine derivatives, in good overall yield in enantiomerically pure form.

The initial examination into the Lewis acid promoted reaction of ketene silyl acetals derived from acetate met with disappointing result, and the desired addition products were obtained in very low yield despite the use of a variety of Lewis acids.

The addition reaction of ester enolate was examined using the lithium enolate of *t*-butyl acetate. When the reaction was carried out with 2.5 equiv. of the lithium enolate, the addition product **5** was obtained in 41% yield. The yield of the adduct was increased

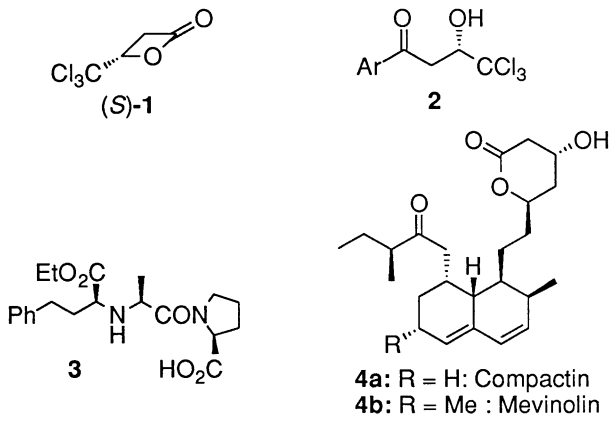
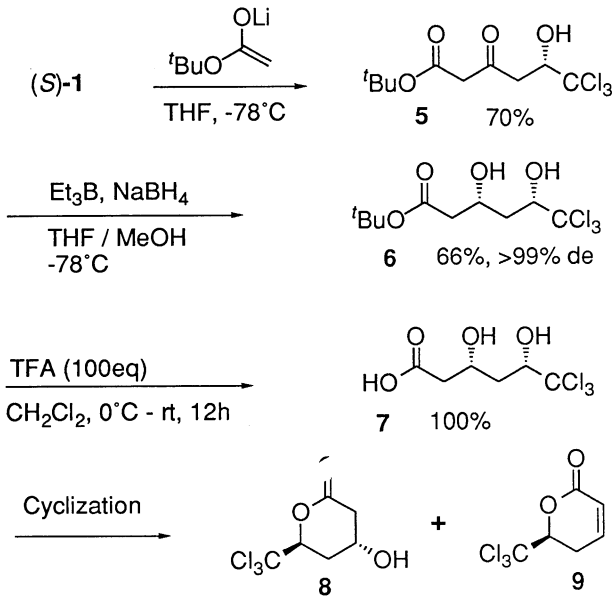


Figure 1.

up to 70% using 5.0 equiv. of the lithium enolate, in which the enantiomeric purity of the adduct was >99% ee.[7] The adduct **5** was then subjected to the *syn*-reduction using Et_3B-$NaBH_4$ procedure,[8] and the *syn*-diol **6** was obtained in 66% yield with >99% de as determined by GLC analysis (SE-30, 50 m). Hydrolysis of the *t*-butyl ester moiety of **6** with trifluoroacetic acid gave dihydroxyacid **7** in quantitative yield.

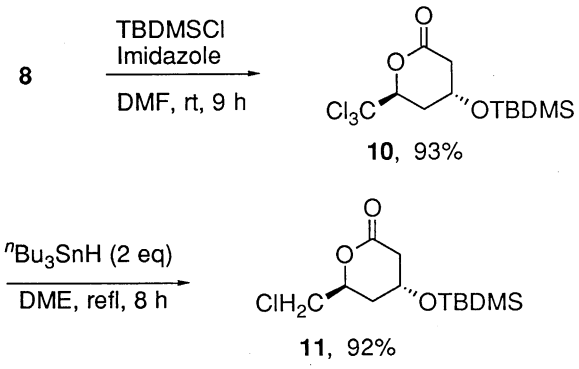
The subsequent cyclization into lactone **8** was sensitive to the reaction conditions, and therefore a variety of conditions were investigated. The cyclization at room temperature in the presence of hydrochloric acid underwent rather sluggishly to give **8** in 28%



Scheme 1.

yield after 168 h, and the reaction at elevated temperature gave the dehydrated α,β-unsaturated γ-varelolactone **9** in moderate yield. The best result was obtained when the cyclization was carried out in toluene in the presence of hydrochloric acid and molecular sieves 3A at 50 °C for 24 h, and the γ-varelolactone **8** was obtained as a sole product in 85% yield.[9,10]

The TBDMS ether **10** was readily obtained in 93% yield on treatment of the lactone **8** with TBDMSCl / imidazole in DMF at room temperature for 9 h. Selective reduction of the trichloromethyl group into monochloro analogue was carried out with tributylstannan in refluxing DME for 8 h, and the monochloride **11** was obtained in 92% yield.[11,12] The lactone **11** is a good precursor for the synthesis of a series of potent inhibitors of HMG-CoA reductase.[13]



Scheme 2.

In conclusion the present procedure for the preparation of β-hydroxy-γ-varelolactones offers a simple and rapid entry into this useful class of compounds in enantiomerically pure form. Since both (*S*)- and (*R*)-β-trichloromethyl-β-propiolactnes are readily available in enantiomerically pure forms, the present methodology will apply to the synthesis of β-hydroxy-γ-varelolactones in both enantiomeric forms on large scales.

References and Notes

1 a) See for example, T.-J. Lee, W. J. Holtz, and R. L. Smith, *J. Org. Chem.*, **47**, 4750 (1982). b) M. Sletzinger, T. R. Verhoeven, R. P. Volante, J. M. McNamara, E. G. Corley, and T. M. H. Liu, *Tetrahedron Lett.*, **26**, 2951 (1985). c) B. D. Roth, D. R. Sliskovic, and B. K. Trivedi, *Ann. Rep. Med. Chem.*, **24**, 147 (1989). d) G. Beck, K. Kesseler, E. Baader, W. Bartmann, A. Bergmann, E. Granzer, H. Jendralla, B. v. Kerekajarto, R. Krause, E. Paaulus, W. Schubert, and G. Wess, *J. Med. Chem.*, **33**, 52 (1990).

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4 T. Fujisawa and T. Sato, *J. Synth. Org. Chem. Jpn.*, **40**, 618 (1982), and the references cited therein.

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6 The enantiomeric purity of the recrystallized (*S*)-β-trichloromethyl-β-propiolactone from cyclohexane was determined to be >99% ee by GLC analysis using a chiral stationary column (Chiraldex G-TA, 20 m). Cf. H. Wynberg and E. G. J Staring, *J. Am. Chem. Soc.*, **104**, 166 (1982). H. Wynberg and E. G. J. Staring, *J. Org. Chem.*, **50**, 1977 (1985). H. Wynberg and E. G. J. Staring, *J. Chem. Soc., Chem. Commun.*, **1984**, 1181. P. E. F. Ketelaar, E. G. J. Staring, and H. Wynberg, *Tetrahedron Lett.*, **26**, 4665 (1985).

7 A typical procedure for the reaction of (*S*)-β-trichloromethyl-β-propiolactne with the lithium enolate derived from *t*-butyl acetate: To a solution of LDA (31.5 mmol) in THF (28 mL) was added a solution of *t*-butyl acetate (4.22 mL, 31.5 mmol) in THF (5 mL) at -78 °C, and the mixture was stirred -78 °C for 30 min. A solution of (*S*)-β-trichloromethyl-β-propiolactne (1.2 g, 6.3 mmol) in THF (3.5 mL) was added at -78 °C. After stirring at -78 °C for 3 h, the mixture was quenched by adding a saturated aqueous NH_4Cl. Usual work up and purification by silica gel chromatography gave the adduct as a colorless oil (1.35 g, 70%). The enantiomeric purity was determined to be >99% ee by GLC analysis (Chiraldex G-TA, 20 m).

8 K. Narasaka and F. C. Pai, *Tetrahedron*, **40**, 2233 (1984).

9 Cyclization was carried out by adding 0.1M (1 M = 1mol dm^{-3}) aqueous HCl (0.06 mL) to a toluene (9.0 mL) solution of the β,δ-dihydroxyacid **7** (35.8 mg, 0.14 mmol). Molecular sieves 4A (132 mg) was added to the solution, and the whole mixture was stirred at 50 °C for 24 h. Usual work-up gave lactone **8** (28.3 mg, 85%) as a sole product. Cf. J. E. Lynch, R. P. Volante, R. R. Wattley, and I. Shinkai, *Tetrahedron Lett.*, **28**, 1385 (1987).

10 ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.95-2.10 (m, 3H), 2.60-2.75 (m, 2H), 4.50-4.63 (m, 1H), 5.18 (dd, 1H, J = 3.63 and 11.21 Hz); $[\alpha]_D^{23}$ -10.8 (c 0.78, $CHCl_3$).

11 C. E. Song, J. K. Lee, S. H. Lee, and S.-g. Lee, *Tetrahedron: Asymm.*, **6**, 1063 (1995).

12 ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.79 (s, 9H), 1.77-1.91 (m, 2H), 2.52 (unresolved d, 2H, J = 3.30 Hz) 3.59 (dd, 1H, J = 3.96 and 11.71 Hz), 3.68 (dd, 1H, J = 5.28 and 11.71 Hz), 4.28-4.30 (m, 1H), 4.80-4.89 (m, 1H); $[\alpha]_D^{23}$ -12.6 (c 0.86, $CHCl_3$). The enantiomeric purity was determined to be >99% ee by GLC (Chiraldex G-TA, 20 m).

13 Cf. Y. L. Yang, S. Manna, and J. R. Falck, *J. Am. Chem. Soc.*, **106**, 3811 (1984).