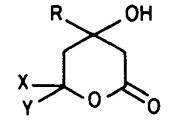
A New Flexible Synthesis of (*R,S*)-Mevalonolactone

Patrizia Ferraboschi,[a] Renato Canevotti, Paride Grisenti, and Enzo Santaniello*
Dipartimento di Chimica e Biochimica Medica and [a] Istituto di Endocrinologia, Facoltà di Farmacia, Università di Milano — I-20133 Milano, Italy

By selective ozonolysis of the diene (**5**), a new synthesis of (*R,S*)-mevalonolactone (**1a**) has been developed, which can be adapted to other compounds related to (**1a**). This has been exemplified by the synthesis of the monodeuteriated triol (**4d**) and dideuteriated mevalonolactone (**1d**).

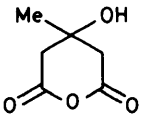
Several syntheses of mevalonolactone (**1a**) are currently available in the literature,[1] mostly concentrated on introducing isotopic labelling into the molecule for biosynthetic studies. Recently, the high yielding synthesis of Scott and Shishido[2] has been extensively studied by other authors,[1,3] in order to clarify important aspects of the synthesis. These studies mainly concentrated on the two key steps, *i.e.* the formation of the anhydride (**2**)[1,3] and its reduction by sodium borohydride.[3]

In order to study new chiral syntheses of (*R*)- and (*S*)-(**1a**), it was desirable to have an easy preparation of both the triol (**3**) and diol (**4a**). For the synthesis of the triol (**3**), we could rely on the method described by Fetizon and co-workers,[4] which we have already used for the preparation of tetradeuteriated mevalonolactone (**1b**).[5] However, we found that ozonolysis procedures are sometimes irreproducible because of changes in ozone concentration and flow rate, and, consequently, reaction times. However by using one type of ozone generator we could repeat Fetizon's experimental procedure, whereas in trying to adapt the same conditions to a smaller apparatus, we could only achieve modest yields of the desired triol (**3**) in dichloromethane as solvent.† Lowering the ozonolysis temperature to −50 °C gave almost quantitative yields of the triol (**3**) (20—30 min, until the classical blue colour appeared). Under our experimental conditions, we observed that selective cleavage of one double bond of the diene (**5**) could be achieved by ozonolysis at −78 °C (CH_2Cl_2, 7 min). After evaporation of the solvent under nitrogen, the intermediate ozonide was directly reduced to the diol (**4a**) by $LiAlH_4$ in anhydrous tetrahydrofuran (THF)‡ and under these experimental conditions, only small amounts (< 10%) of the triol (**3**) were formed. Reduction of the ozonide by $NaBH_4$ in methanol gave lower recovery of the diol (**4a**) owing to the problems associated with the aqueous work-up. Extracting the reaction mixture with water completely removed the triol (**3**). Essentially the pure diol (**4a**) could be obtained in 78% from the diene (**5**). Selective ozonolysis of the diene (**5**) could also be suitable for the preparation of the aldehyde (**4b**), reducing the ozonide in a clean way with polymer-supported triphenylphosphine (PTPP)[6] (86% yield). In contrast, direct chromic oxidation of the crude ozonide led to the acid (**4c**) in lower yeilds, whereas good yields were achieved by Ag_2O oxidation of the aldehyde (**4b**) (82%). The immediate synthetic application of the enediol (**4a**) was, of course, a new preparation of mevalonolactone (**1a**). Thus, although the C-1 hydroxy group could be safely protected, the shortest route

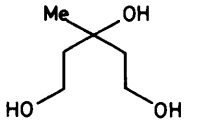


(**1**)

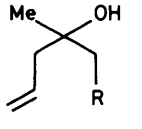
a; X = Y = H, R = Me
b; X = ^{2}H, Y = H, R = C^2H_3
c; X = ^{2}H, Y = H, R = Me
d; X = Y = ^{2}H, R = Me



(**2**)

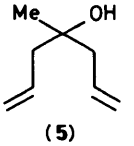


(**3**)

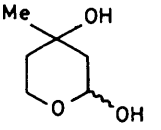


(**4**)

a; R = CH_2OH
b; R = CHO
c; R = CO_2H
d; R = CH^2HOH
e; R = CO_2Me
f; R = C^2H_2OH



(**5**)



(**6**)

from the unprotected diol (**4a**) was realized as follows. The residual double bond in the diol (**4a**) was cleaved (dichloromethane–acetic acid, 10:1, −50 °C) and reduction with PTPP of the ozonide[6] afforded the diol (**6**) (85% yield), which was directly oxidized to compound (**1a**)[7] (pyridinium chlorochromate in dichloromethane,[8] 82%). By this simple synthetic sequence, mevalonolactone (**1a**) could be isolated in 54% yield from the diene (**5**). It should be pointed out that this synthetic sequence, although not optimized with respect to yield, compares favourably with other cited methods. Further, using a difunctional intermediate, such as the mono-ozonide corresponding to the diol (**4a**) or (**4b**), can be seen as the ideal starting material for molecules other than compound (**1a**) (mevaldic acid,[9] for instance). As an application of this concept, the method can serve as a rather flexible preparation of labelled mevalonolactone. In fact, by Fetizon's method[4] only one deuterium can be placed at C-5, whereas by Scott's synthesis two deuterium atoms are obligatorily introduced at C-5. In our case, starting from the diene (**5**), reduction of the ozonide by $LiAl^2H_4$ afforded the

† If the reaction is carried out at −5 °C, several problems are encountered such as prolonged reaction times and evaporation of solvent, *etc.*

‡ Ozonolysis was generally carried out on a maximum amount of 5 mmol of the diene (**5**) so that the reaction times, a critical factor for yields reproducibility, were constant. Larger scale ozonolyses were simulated by carrying out a number of standard (5 mmol) reactions, bulking the final reaction mixtures and processing them as described in the Experimental section.

monodeuteriated diol (**4d**) in 76% yield, which could be eventually converted into 5-monodeuteriated mevalonolactone (**1c**) as previously described. On the other hand, oxidation of the aldehyde (**4b**) to the acid (**4c**), esterification with diazomethane to the ester (**4e**), and $LiAl^2H_4$ reduction of the ester (**4e**) afforded the 5-dideuteriated diol (**4f**) in 55% yield from the diene (**5**) (complete introduction of the label). The conversion into the labelled compound (**1d**) may be followed by a well established experimental procedure. Further applications of this method are in progress in our laboratory and aim at the chiral synthesis of compound (**1a**).

Experimental

Distillations for analytical purposes were performed with a glass tube oven Buchi GKR-50. ^1H N.m.r. spectra were recorded on a Varian 360 L spectrometer for solutions in $CDCl_3$ using Me_4Si as internal standard. Mass spectra were recorded on a LKB 2091 gas chromatograph–mass spectrometer. The progress of all reactions and column chromatography was monitored by t.l.c. on E. Merck silica gel HF_{254} plates visualized by u.v. absorption or exposing plates to iodine vapour or spraying with a 5% ethanolic solution of phosphomolybdic acid. Gas chromatographic analyses were carried out on a Carlo Erba Fractovap 2001 (column 1% OV 17), carrier N_2. Ozonolyses were carried out using a Fischer ozone-generator Model 501 (Zurich, Switzerland).

4-*Methylhepta*-1,6-*diene*-4-*ol* (**5**).—The diene was prepared essentially according to ref. 1 in 70—75% yield, except that evaporation of solvent and distillation of the diene (**5**) were carried out at atmospheric pressure; b.p. 140—142 °C.

3-*Methylhex*-5-*ene*-1,3-*diol* (**4a**).—A solution of the dienol (**5**) (0.5 g, 4 mmol) in anhydrous dichloromethane (5 ml) was ozonized at −78 °C (7 min, flow rate 20l h^{-1}). After evaporation of the solvent under nitrogen, anhydrous THF (5 ml) was added and the solution carefully added to a suspension of $LiAlH_4$ (0.75 g, 21 mmol) in anhydrous THF (10 ml). After 12 h at room temperature, water (0.75 ml), 15% aqueous NaOH (0.75 ml), and water (2.3 ml) were sequentially added. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure to afford the title compound (**4a**) (0.41 g, 78%), b.p. 175—180 °C (20 mmHg) (Found: C, 64.8; H, 10.9. Calc. for $C_7H_{14}O_2$: C, 64.6; H, 10.8%); δ 1.30 (3 H, s, Me), 1.80 (2 H, t, CH_2), 2.20—2.50 (2 H, m, $=CHCH_2$), 3.80—4.10 (1 H, m, exchangeable), 4.00 (2 H, t, CH_2O), and 4.95—6.35 (3 H, m, $H_2C=CH$). For bigger preparations, several ozonolyses were repeated on a 5 mmol scale, the reaction mixtures being kept separately at −78 °C and then bulked and treated as above.

2,3,5,6-*Tetrahydro*-4-*methylpyran*-2,4-*diol* (**6**).—A solution of the diol (**4a**) (0.585 g, 4.5 mmol) in anhydrous dichloromethane (5 ml) and acetic acid (0.5 ml) was ozonized at −50 °C until the solution became blue. The excess of ozone was removed under nitrogen and the solution was added to a suspension of PTPP (1.6 g, 4.8 mmol) in dichloromethane (5 ml). After being stirred for 4 h at room temperature, the mixture was filtered and the filtrate treated with an excess of solid sodium hydrogen carbonate. The latter was filtered off, and the filtrate evaporated under reduced pressure to leave the diol (**6**) (0.5 g, 85%), which was essentially pure; δ 1.25 (3 H, s, Me), 1.55—2.00 (2 H, m, CH_2), 2.25—2.45 (2 H, m, CH_2), 3.75—4.15 (3 H, m, CH_2O and exchangeable H), and 4.85 (1 H, s, OCHO).

Mevalonolactone (**1a**).—A solution of the diol (**6**) (0.5 g, 3.8 mmol) in anhydrous dichloromethane (5 ml) was added to a suspension of pyridinium chlorochromate (1.6 g, 7.5 mmol) and sodium acetate (0.06 g, 0.7 mmol) in anhydrous dichloromethane (15 ml). After being stirred for 6 h at room temperature, the mixture was filtered through Celite and the filtrate evaporated under reduced pressure to leave a residue which was purified on a Florisil column. The title compound (**1a**) was obtained (0.41 g, 82%) essentially pure. A sample was distilled at b.p. 150—155 °C (5 mmHg) (Found: C, 55.6; H, 7.9. Calc. for $C_6H_{10}O_3$: C, 55.4; H, 7.7%); δ 1.40 (3 H, s, Me), 1.95 (2 H, t, CH_2), 2.60 (2 H, s, $COCH_2$), and 4.15—4.70 (2 H, m, CH_2O); *m/z* 130 (M^+), 115, 102, 85, and 71.

[1-$^2H_1$]-3-*Methylhex*-5-*ene*-1,3-*diol* (**4d**).—The diene (**5**) (0.5 g, 4 mmol) was ozonolized and the product reduced with $LiAl^2H_4$ (0.75 g, 19 mmol) in anhydrous THF (10 ml) to give, after work-up, the title compound (**4d**) (0.4 g, 76%), b.p. 175—180 °C (20 mmHg) (Found: C, 64.2; H, 11.6. Calc. for $C_7H_{13}{}^2HO_2$: C, 64.1; H + ^2H, 11.5%); δ 1.25 (3 H, s, Me), 1.75 (2 H and 1 H exchangeable, d, CH_2C^2HH), 2.35 (2 H, d, $=CHCH_2$), 3.95 (1 H, t, CHO), and 4.95—6.35 (3 H, m, $H_2C=CH$); *m/z* 131 (M^+), 116, 104, 90, and 85.

3-*Hydroxy*-3-*methylhex*-5-*enal* (**4b**).—A solution of the diene (**5**) (0.56 g, 4.4 mmol) in anhydrous dichloromethane (5 ml) was ozonized at −78 °C for 5 min. The excess of ozone was removed under nitrogen and the solution was added to a suspension of PTPP (1.48 g, 4.5 mmol) in dichloromethane (5 ml). After being stirred for 2 h at room temperature, the mixture was filtered and the filtrate treated with an excess of solid sodium hydrogen carbonate. The latter was filtered off, and the filtrate evaporated under reduced pressure to leave a residue of the aldehyde (**4b**) (0.48 g, 86%), which was essentially pure; b.p. 140 °C (17 mmHg) (Found: C, 65.7; H, 9.5. $C_7H_{12}O_2$ requires C, 65.6; H, 9.4%); δ 1.30 (3 H, s, Me), 2.35 (2 H, d, CH_2), 2.60 (2 H, s, CH_2CO), 4.95—6.20 (3 H, m, $CH_2=CH$), 9.90—10.0 (1 H, m, CHO).

Methyl 3-*Hydroxy*-3-*methylhex*-5-*enoate* (**4e**).—To a solution of the aldehyde (**4b**) (0.45 g, 3.5 mmol) in a mixture of dioxane (10 ml) and water (10 ml), a solution of silver nitrate (0.6 g, 3.5 mmol) in water (10 ml) and a solution of sodium hydroxide (0.64 g, 1.6 mmol) in water (10 ml) were sequentially added. After being stirred for 2 h at room temperature, the mixture was acidified (2M HCl) to pH 1, and the products were extracted with diethyl ether (3 × 30 ml). Work-up of the latter gave the acid (**4c**) (0.41 g, 82%); δ 1.30 (3 H, s, Me), 2.35 (2 H, d, $CH_2CH=$), 2.60 (2 H, s, $COCH_2$), 4.95—6.15 (3 H, m, $CH=CH_2$), and 7.45 (1 H, exchangeable). To a solution of the above acid (0.41 g, 2.8 mmol) in diethyl ether (5 ml) cooled in an external ice-bath, an excess of freshly prepared solution of diazomethane in diethyl ether was added dropwise. Removal of excess of diazomethane under nitrogen and evaporation of solvent, quantitatively afforded the ester (**4e**) (0.44 g) (Found: C, 60.9; H, 9.0. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%); δ 1.25 (3 H, s, Me), 2.35 (2 H, d, $CH_2CH=$), 2.50 (2 H, s, CH_2CO), 3.75 (3 H, s, OMe), and 4.95—6.20 (3 H, m, $CH_2=CH$).

[1-$^2H_2$]-3-*Methylhex*-5-*ene*-1,3-*diol* (**4f**).—A solution of the ester (**4e**) (0.2 g, 1.3 mmol) in anhydrous THF (5 ml) was added to a suspension of $LiAl^2H_4$ (0.14 g, 3.5 mmol) in anhydrous THF (10 ml). After 1 h at room temperature and work-up, the title compound (**4f**) (0.134 g, 78%) was obtained; b.p. 175—180 °C (20 mmHg) (Found: C, 63.7; H, 12.2. Calc. for $C_7H_{12}{}^2H_2O_2$: C, 63.6; H + ^2H, 12.1%); δ 1.25 (3 H, s, Me), 2.35 (2 H, d, $=CHCH_2$), 3.75—4.00 (3 H, m, $CH_2C^2H_2$ and exchangeable), and 4.95—6.15 (3 H, m, $H_2C=CH$); *m/z* 132 (M^+), 117, 105, 91, and 85.

[5-$^2H_2$]-*Mevalonolactone* (**1d**).—Starting from the above

dideuteriated diol (**4f**) (0.09 g, 0.68 mmol) and following the previous procedure (ozonolysis to the diol and pyridinium chlorochromate oxidation), the title compound (**1d**) was obtained (0.063 g, 70%). A sample was distilled at 5 mmHg, b.p. 150—155 °C (Found: C, 54.6; H, 9.2. Calc. for $C_6H_8{}^2H_2O_3$: C, 54.6; H + ^{2}H 9.1%); δ 1.40 (3 H, s, Me), 1.95 (2 H, s, $CH_2C^2H_2$), and 2.60 (2 H, s, $COCH_2$); *m/z* 132 (M^+), 117, 102, 85, and 73.

Acknowledgements

This work was supported by a grant from Ministero della Pubblica Istruzione. We thank Mr. Andrea Lorenzi for mass spectra.

References

1 E. Bardshiri, T. J. Simpson, A. I. Scott, and K. Shishido, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1765, and references cited therein.
2 A. I. Scott and K. Shishido, *J. Chem. Soc., Chem. Commun.*, 1980, 400.
3 P. Lewer and J. MacMillan, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1417.
4 M. Fetizon, M. Golfier, and J. M. Louis, *Tetrahedron*, 1975, **31**, 171.
5 G. Cighetti, E. Santaniello, and G. Galli, *Anal. Biochem.*, 1981, **110**, 153.
6 P. Ferraboschi, C. Gambero, M. Nasr Azadani, and E. Santaniello, *Synth. Commun.*, 1986, **16**, 667.
7 S. Takano, M. Morimoto, and K. Osagawara, *J. Chem. Soc., Chem. Commun.*, 1984, 82.
8 E. J. Corey and J. D. Suggs, *Tetrahedron Lett.*, 1975, 2647.
9 P. Blattmann and J. Retey, *J. Chem. Soc., Chem. Commun.*, 1970, 1393.

Received 23*rd July* 1986; *Paper* 6/1499