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STUDIES ON ASYMMETRIC SYNTHESIS OF β-HYDROXY-δ-LACTONE INHIBITORS OF HMGCoA REDUCTASE 1. A NEW PREPARATION OF THE LACTONE MOIETY OF COMPACTIN

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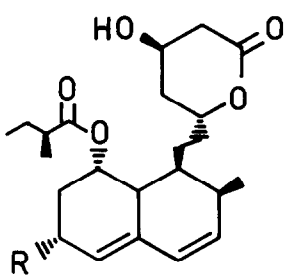
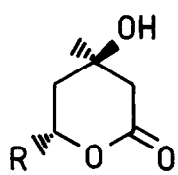
Abstract: a new strategy for the preparation of chiral β-hydroxy-δ-lactone inhibitors of HMGCoA reductase is outlined: in particular the compactin lactone moiety has been elaborated by asymmetric epoxidation of the appropriate allylic alcohol and subsequent introduction of the second chiral center via a new $Ti(OiPr)_4$ mediated reduction of ß-hydroxy ketones.

The use of compounds, having a lactone system resembling that of the 3-hydroxy-3-methyl coenzyme A reductase (the major rate limiting enzyme in the cholesterol biosynthesis) as potent hypocholesterolemic agents has been extensively studied in the last years: in particular several biological studies on natural products such as compactin 1[1] and mevinolin 2[2] has prompted extensive synthetic investigation[3] also on various mevalonolactone analogs such as 3[4] and 4[5]. More recently impressive works by Merck Sharp & Dohme appeared[6], describing the chiral and racemic syntheses of more than one hundred analogs of 1 and 3, and showing the high interest for such compounds due the their biological properties.



1 R=H

2 R=CH_3



3 R=$CH_2-CH_2-C_6H_4-X$

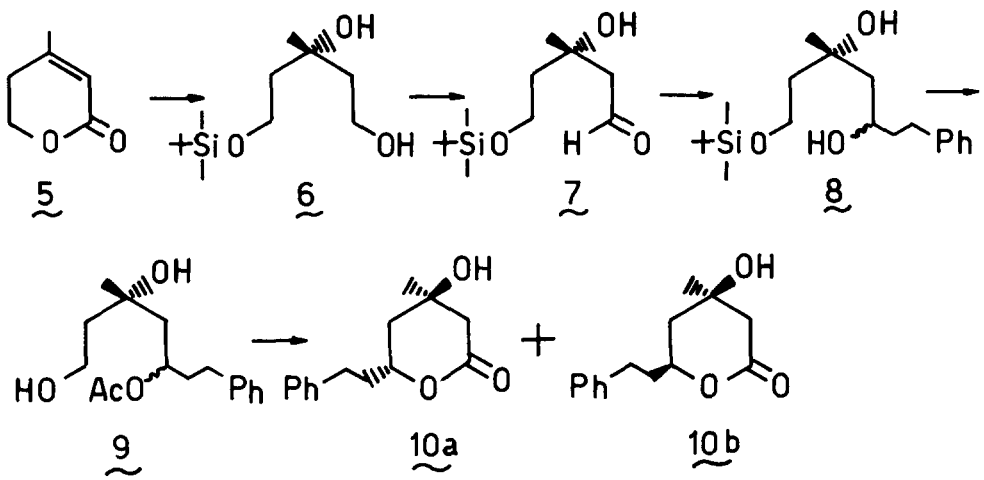
4 R=$CH_2-S-S-Ph$

We have recently reported[7] a new asymmetric synthesis of mevalonolactone; we have then thought that the same strategy could be adopted to prepare optically active compounds such as 3 (X=H) and a model lactone ring system of 1 and 2.

The easily prepared anhydromevalonolactone 5[8] (scheme 1) was therefore transformed into the known diol 6[7] by a sequence involving the enantioselective epoxidation[9] of the appropriate

allylic alcohol[10]. 6 was then oxidized by a modified PCC procedure[11] to the aldehyde 7 in 60% yield. Addition of 7 to a solution of ethylphenyl magnesiumbromide (2.5 eq.) in ether at

SCHEME 1



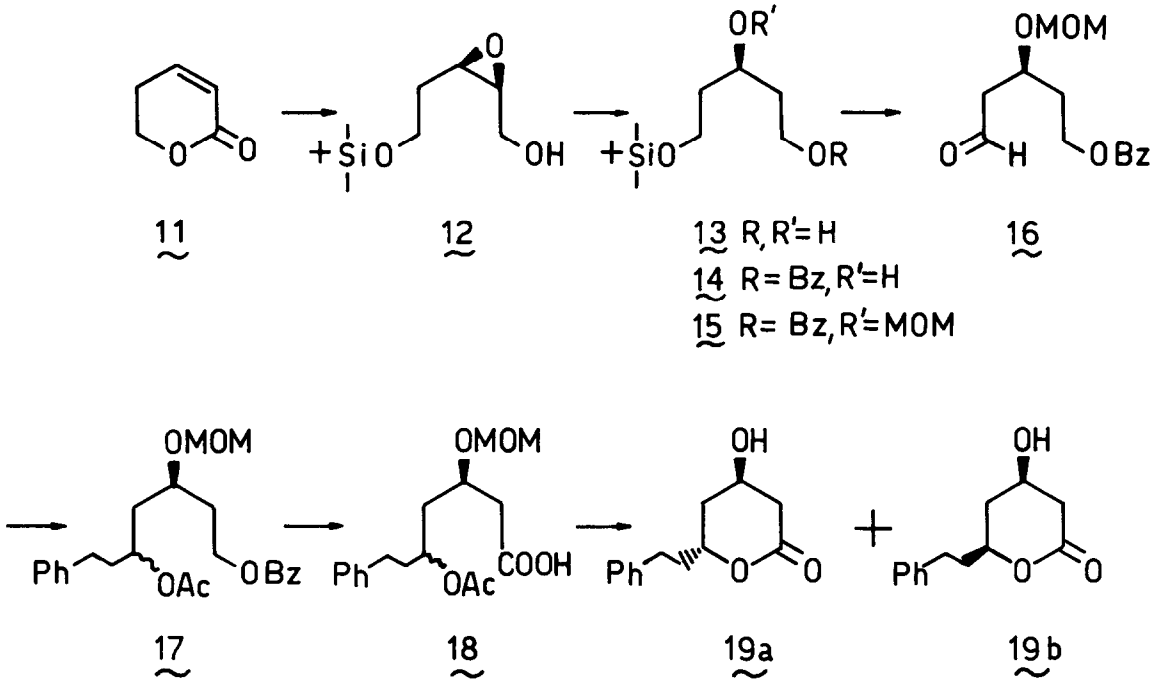
room temp. gave a mixture of the epimeric alcohols 8 in 95% overall yield. The subsequent acetylation of the secondary hydroxyl function and desilylation of the primary one (TBAF, room temp., 30 min.) gave a mixture of alcohols 9 in 95% overall yield.

The oxidation of 9[12] to the corresponding acid was followed by deacetylation (MeOH, NaOH 2N, 12 h., room temp.), acidification and extraction (EtOAc) of the concentrated aqueous mixture. The two diastereomeric lactones were easily chromatographed, affording the less polar 10a ($[\alpha]_D^{20}$ = +46°) and the more polar 10b ($[\alpha]_D^{20}$ = -62.3°) in a 2:1 ratio[4,13].

The successfull preparation of 10a and 10b prompted us to plan the synthesis, along the same strategy, of the β-hydroxy-δ-lactone moiety of compactin 1; starting material of choise was the chiral epoxy alcohol 12 easily prepared from the commercial available lactone 11[14] (see scheme 2).

Regioselective[15] opening of 12 (Red/Al, toluene, -20°C, 2 h.) afforded in 75% yield exclusively the diol 13 which was transformed by standard procedure into compound 15 via the monobenzyl 14 (69% overall yield). 15, which can be considered a new C_5 chiral building block, was then desilylated (TBAF, THF, room temp.) and oxidized (PCC/Al_2O_3, benzene, room temp.) to the aldehyde 16 (78% yield). Addition of 16 to a solution of ethylphenyl magnesium bromide (1.5 eq.) in ether at room temp. afforded a diastereomeric mixture of alcohols which was acetylated to 17 (85% yield). Debenzylation (Pd/C, H_2, MeOH room temp., 12 h.) and oxidation[12] afforded the acid 18; the successive alkaline hydrolysis (MeOH, NaOH 4N, 8 h.) and acidification (HCl 2N, 2 h.) gave a mixture of two products (35% overall yield from

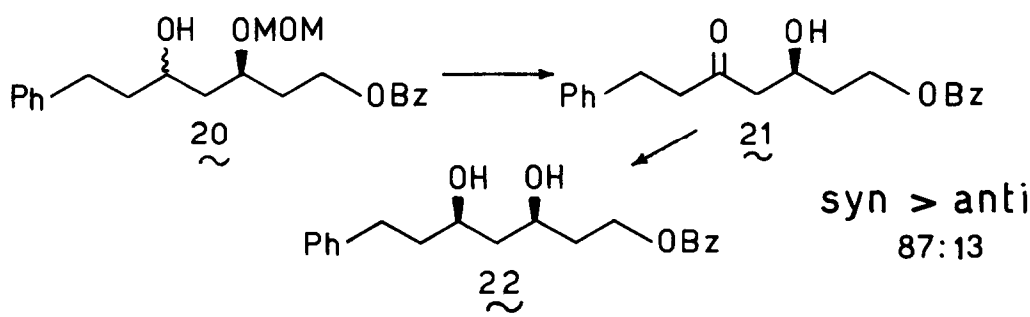
SCHEME 2



17) which were separated by HPLC to give the diastereomeric lactones 19a and 19b[16] in a 2:1 ratio.

Since the diastereoselective introduction of the chiral center at C_5 was quite poor, we used the β-hydroxy ketone 21 (obtained from 20 by PCC oxidation and selective removal of the MOM ether with Me_2BBr[17] 80% overall yield, Scheme 3) as starting material to obtain the correct syn diol 22.

SCHEME 3



After exaustive attempts with the known methods[18], we have found that the best result was obtained with a novel procedure, involving $Ti(OiPr)_4$ as coordinating metal and $NaBH_4$ in THF at -78°C (87:13 ratio syn-anti, better than 82:18 obtained with DIBAL procedure[18b]). Along this way the new procedure to obtain 1,3 diols is under intensive investigation on several model ß-hydroxy ketones; on the other hand, other compactin analogs are being prepared te demonstrate the flexibility of our strategy and detailed experimental will be reported in a forthcoming paper.

We thank Mr. G. Frashey and Mr. F. Piccioni for the excellent spectroscopic measurements.

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11. A solution of diol 6 in anhydrous CH_2Cl_2 was added slowly to a stirring mixture of PCC (4 eq.) in CH_2Cl_2, Py and molecular sieves. In this way the yield of the PCC oxidation raised from low to good; unfortunately all others procedures so far attempted (e.i. the Swern oxidation) failed in our hands.
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13. The enantiomeric excess for 10a, determined on a Bruker WP80SY (90 MHz) using $Eu(hfc)_3$ as shift reagent, was measured to be 84.5%.
14. 12 was the enantiomer of the epoxy alcohol prepared according to ref. 10. The enantiomeric excess of 12 was shown to be > 98%, estimated by GLC analysis of the corresponding MPTA ester (Mosher derivative).
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16. 19a. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7-7.3 (m, 5H); 4.70 (m, 1H); 4.39 (m, 1H); 2.5-3.0 (m, 4H); 1.70-2.15 (m, 5H). $[\alpha]_D^{20°}$ = + 45.6.
19b. ^{1}H-NMR: δ 7-7.3 (m, 5H); 4.30 (m, 2H); 3.9-4.1 (s, 1H); 2.6-3.0 (m, 3H); 2.4-2.6 (m, 1H); 1.7-2.3 (m, 4H). $[\alpha]_D^{20°}$ = -43.6 °.
The ^{1}H-NMR of 19a was in complete agreement with the data kindly provided by Prof. D.L.J. Clive on the same product prepared by other route (see M. Majewski, D.L.J. Clive and P.C. Anderson, Tetrahedron Lett. 25, 2101 (1984)).
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19. All new compounds gave satisfactory ^{1}H-NMR and H.R. MS data.

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