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PREPARATION OF ETHYL 5(S),6-EPOXY-3(R)-(METHOXYMETHOXY)HEXANOATE: A KEY CHIRAL INTERMEDIATE FOR MEVINOLIN AND COMPACTIN.

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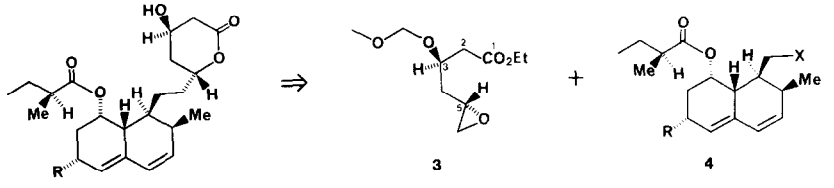
ABSTRACT: The synthesis of Ethyl 5(S),6-Epoxy-3(R)-(methoxymethoxy)hexanoate, a key chiral synthon for the β-hydroxy-δ-lactone portion of Mevinolin and Compactin, via a regiospecific ring opening of a tetrahydrofuran derivative by dimethylboron bromide, is described.

Mevinolin 1[1] and Compactin 2[2] have attracted considerable interest from the scientific community because of their biological profiles as potent hypocholesterolemic agents[3], as well as their unique structural features. Syntheses of these natural products[4], their analogs[5] and precursors[6,7] have been pursued. Herein, we would like to report on the efficient synthesis of the primary epoxide 3, an important chiral precursor to the β-hydroxy-δ-lactone moiety.



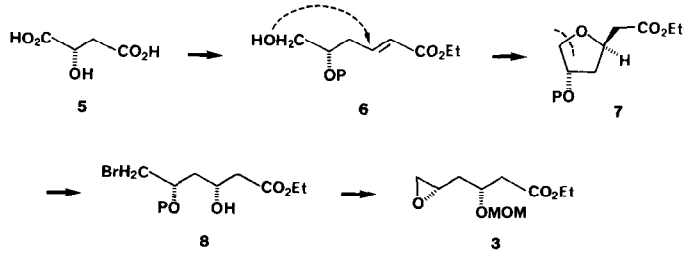
1 R = Me
2 R = H

3

4

X = Cl, Br, SO_2Ph

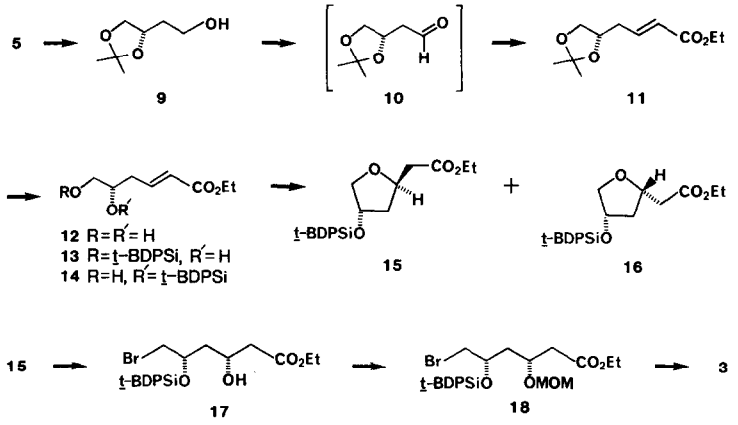
Dimethylboron bromide has been shown to be a highly reactive reagent for the cleavage of carbon-oxygen bonds,[8] especially useful in our context due to its ability to ring open 2-substituted tetrahydrofuran derivatives in a regiocontrolled fashion.[8a] This broadens the synthetic utility of chiral tetrahydrofuran derivatives[9] for the stereoselective generation of chiral acyclic compounds, as illustrated



5 6 7 8 3

below. Hence, our synthetic strategy for obtaining the primary epoxide 3 was based on the following. Readily available (S)-malic acid 5 ("chiron"[10]) was chosen as the starting material on the basis that its hydroxyl group could be transformed into the C-5 oxygen of 3. The remaining chiral center of our targeted compound, C-3 of 3, could than be generated from an intramolecular Michael addition of 6 (P = protecting group) to afford the thermodynamically preferred "trans" tetrahydrofuran derivative 7.[9] The key regioselective ring opening of 7 would then give rise to the β-hydroxy ester 8 which contains all of the necessary asymmetry and functionalities for further elaboration into epoxide 3. The synthesis of 3 was sucessfully performed using this approach and the results are summarized below.

Reduction of (S)-malic acid 5 (3.0 equiv. BH_3·THF, THF, 0°C to room temperature) and ketalization (acetone, pTsOH·H_2O) of the resultant crude material gave the protected triol 9 (80%).[11,12] Swern oxidation[13] of 9 generated the aldehyde 10 which, without isolation, was further reacted with Ph_3PCHCO_2Et (2.5 equiv., 0°C to room temperature, 3h) to afford the trans-α,β-unsaturated ester 11, $[\alpha]_D$ -18.0 (c 2.43, MeOH) in 84% yield.[14] Hydrolysis of the acetonide moiety (1N HCl, aq. THF, room temperature, 18h) and selective silylation[15] (tBuPh_2SiCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 18h) of the resultant diol 12 cleanly generated the primary tert-butyldiphenylsilyl (t-BDPSi) ether 13, $[\alpha]_D$ -10.0 (c 1.23, MeOH).



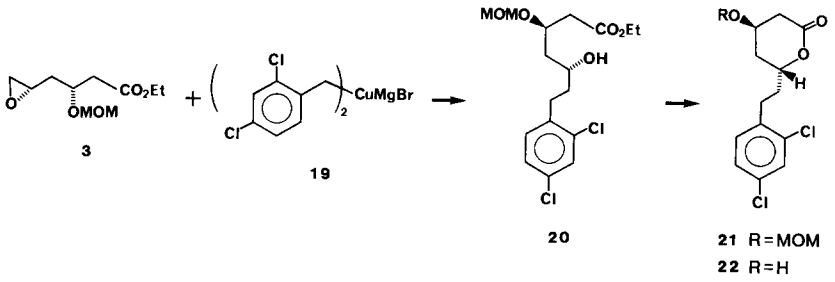
We reasoned that exposure of 13 to base would establish an equilibrium between it and the silyl migration product, 14.[16] In spite of the steric factors disfavoring 14, the equilibrium would be displaced by an ensuing intramolecular Michael addition of the primary hydroxyl group of 14 to the α,β-unsaturated ester, to yield the corresponding tetrahydrofuran derivatives (15 and 16). Thus, treatment of 13 with NaOEt (0.1 equiv., EtOH, room temperature, 2h then reflux 4h) afforded a 2:1 mixture (^{1}H NMR, 250 MHz) of the isomeric cyclic ethers 15 and 16 (87%). The products were then separated by flash chromatography (SiO_2, hexane-ethyl acetate, 95:5) and their stereochemical identities confirmed by ^{1}H NMR nOe.[17] The predominant, less polar component proved to be the desired trans (2R,4S) tetrahydrofuran derivative 15, $[\alpha]_D$ +7.81 (c 2.58, MeOH), whereas the minor component was determined to be the cis (2S,4S)

diasteriomer 16.[18]

Having the key intermediate 15 in hand, the successful completion of our synthetic strategy now depended on a crucial ring opening of the tetrahydrofuran moiety. Although a wide variety of ether cleaving reagents are known[19], few permit the cleavage of 2-substituted tetrahydrofurans. Attempted ring opening of 16 using either TMSI[20], $PhSSiMe_3$[21] or $EtSH{\cdot}AlCl_3$[22] proved unsuccessful and in no cases were useful amounts of isolable products detected. Cleavage of 15 with 2.0 equiv. of dimethylboron bromide (CH_2Cl_2, 0°C, 10 min then room temperature, 2h) proceeded smoothly with complete regioselectivity to afford the bromoalcohol 17 in good yield (82%). The regiochemistry of the product was confirmed by ^{13}C NMR.[23]

Protection of the hydroxyl group of 17 (excess MOM-Cl, iPr_2NEt, DMAP, CH_3CN, -3°C, 24h) gave the MOM ether 18 in excellent yield (94%). Treatment of 18 with 3.0 equiv. of nBu_4NF (THF, room temperature, 3h) directly afforded the desired epoxide 3, $[\alpha]_D$ -31.5 (c 0.98, MeOH) in 80% yield. Coupling of the epoxide with model systems and formation of the lactone ring was accomplished by the following transformations.

Treatment of 3 with the cuprate reagent 19 (1.3 equiv., -78°C, 1h then -23°C, 1h) derived from 2,4-dichlorobenzylmagnesium bromide ($CuBr{\cdot}SMe_2$ in a 1:1 mixture of Et_2O and Me_2S at -78°C, 15min.) afforded the alcohol 20 in quantitative yield. Exposure to $pTsOH{\cdot}H_2O$ (cat. amt.) in benzene gave the corresponding lactone 21 (90%). Subsequent deprotection of 21 with dimethylboron bromide[8b] (4 equiv., -78°C, 1h) proceeded smoothly to give the β-hydroxy-lactone 22, $[\alpha]_D$ +59.7 (c 1.10, $CHCl_3$), (79%).[24]



In summary, an efficient synthesis of the chiral epoxide 3 from (S)-malic acid 5 has been described. The utility of synthetically important tetrahydrofuran derivatives for the preparation of acyclic compounds using the new reagent dimethylboron bromide, and the usefulnes of 3 as an effective synthon for the lactone portion of Mevinolin 1 and Compactin 2 has been exemplified.

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24. The same product has been produced by a different route: $[\alpha]_D$ +63.1°. T.-J. Lee, personal communication.

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