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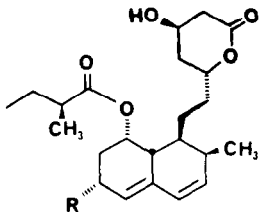
A DIASTEREOSPECIFIC, NON-RACEMIC SYNTHESIS OF A NOVEL β-HYDROXY-δ-LACTONE HMG-CoA REDUCTASE INHIBITOR

M. Sletzinger, T.R. Verhoeven*, R.P. Volante*, J.M. McNamara
E.G. Corley, and T.M.H. Liu

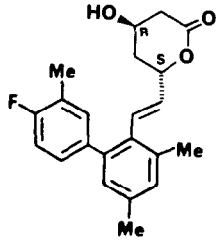
Merck Sharp & Dohme Research Laboratories
Division of Merck and Co., Inc.
Rahway, New Jersey 07065

Abstract: The coupling of acyl anion equivalent 12b with chiral synthon 14, derived from isoascorbic acid, and a highly stereospecific reduction of the resulting β-hydroxy ketone 3 highlight an efficient synthesis of β-hydroxy-δ-lactone 2.

The inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by compactin (1a)[1], mevinolin (1b)[2] and their analogs[3] has been intensely studied. However, investigations concerning potent HMG-CoA reductase inhibitors possessing more varied structural modifications have been less well reported due to a lack of methodology for the synthesis of appropriately substituted β-hydroxy-δ-lactones. We report herein an efficient, stereospecific methodology for the construction of non-racemic β-hydroxy-δ-lactones as illustrated in the total synthesis of 2, a potent inhibitor of HMG-CoA reductase[4].

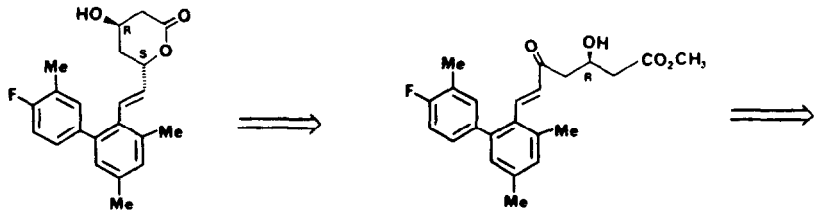


1a: Compactin; R=H
1b: Mevinolin; R=Me



2

Our strategy for the synthesis of 2 is outlined below. We envisioned the introduction of the 3(R)-hydroxyl stereochemistry via coupling of an acyl anion equivalent 4 with an appropriately functionalized "chiral synthon" 5. The desired 3-hydroxyl stereochemistry of 5 should be readily attainable via degradation of isoascorbic acid (6)[5,6]. The 3(R)-hydroxyl function of 3 would then be expected to direct the subsequent reduction of the 5-keto group to the desired 5(S) stereochemistry of 2 according to the procedure of Narasaka[7a]. The remainder of this communication describes the successful completion of this strategy.



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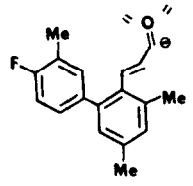

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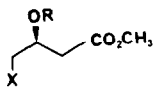

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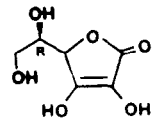

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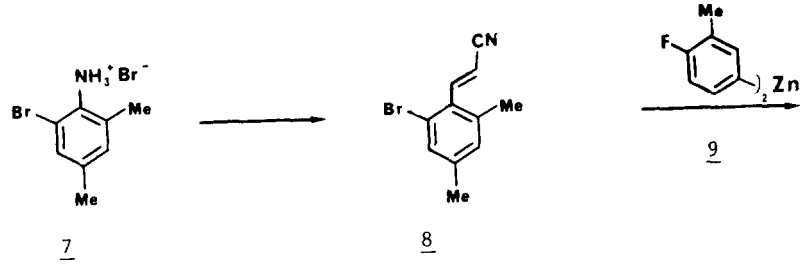
2-Bromo-4,6-dimethylaniline hydrobromide (7), prepared by bromination of 2,4-dimethylaniline (96% yield), underwent diazotization with sodium nitrite-hydrobromic acid (1.25 equiv) and subsequent Meerwein reaction[8] with acrylonitrile (excess) in the presence of cuprous bromide (0.005 equiv) to give E-2-bromo-4,6-dimethylcinnamonitrile (8) as a crystalline solid (72%, m.p. 95-96°). 5-Bromo-2-fluorotoluene was converted to its organozinc derivative 9[9] which was coupled with 8 in the presence of bis-triphenylphosphine nickel dichloride[10] to give the biphenyl α,β-unsaturated nitrile 10 (m.p. 86-87°) in 80% yield after crystallization. Reduction of 10 with diisobutylaluminum hydride (1.1 equiv) in toluene at -45°, followed by acidic workup, gave a 95% isolated yield of biphenyl aldehyde 11 (m.p. 83-86°). Treatment of aldehyde 11 with sodium cyanide (1.5 equiv) in aqueous 3N HCl - acetonitrile (1:1) at 0° gave cyanohydrin 12a, which was converted to the tetrahydropyranyl derivatives 12b in 90% overall yield.



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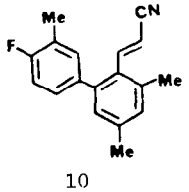

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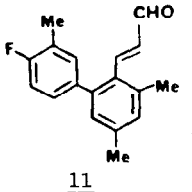

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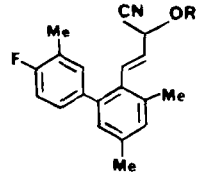
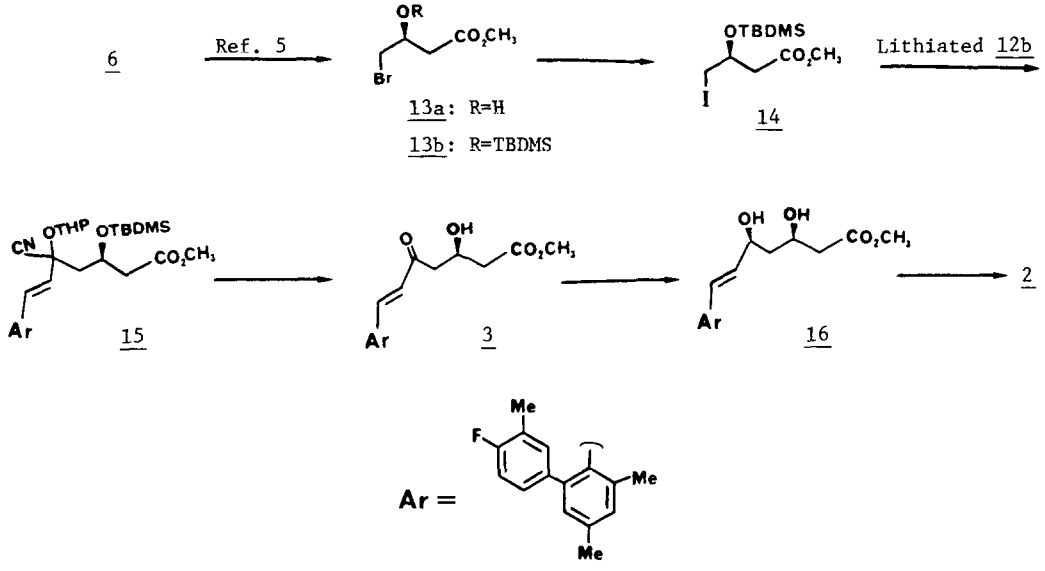


12a: R=H

12b: R=THP

The desired chiral synthon, methyl (S)-4-bromo-3-hydroxybutanoate (13a), was prepared in three steps (60% overall yield) from isoascorbic acid (6) by the methodology described by Bock et. al.[5] for the degradation of ascorbic acid. Bromohydrin 13a was protected as the t-butyldimethylsilyl ether 13b (α_D=-26.4°,c=4.0($CHCl_3$)) by treatment with TBDMS-Cl (1.1 equivalent), imidazole (5.0 equivalent), and 4-dimethylaminopyridine (0.005 equivalent) in dimethylformamide and was then converted to the more reactive protected iodohydrin 14 (α_D=-32.5°,c=4.0,($CHCl_3$)) by reaction with sodium iodide (5.0 equivalents) in refluxing methyl ethyl ketone (90% overall yield from 13a). Iodo ester 14 (1.1 equivalents) was coupled with the acylanion equivalent[11] of 12b (1.0 equivalent, prepared by metalation of 12b at -78° with 1.0 equivalent of n-butyllithium) in the presence of 2.0 equivalents of 1,3-dimethyl-2-imidazolidinone at -25° for 2 hr to give a 53% yield of cyanohydrins 15 after chromatography[12]. Removal of the tetrahydropyranyl and t-butyldimethylsilyl groups using acetic acid-water-tetrahydrofuran (4:1:1) at 65° for 48 hr provided an 85% yield of keto-alcohol 3. Highly stereospecific reduction of the 5-keto functionality to the desired 5(S) stereochemistry was effected using sodium borohydride-triethylborane in tetrahydrofuran-methanol (4:1) at -78° giving diol 16 in 90% yield [7,13,14]. Diol ester 16 was then saponified with sodium hydroxide in aqueous methanol, acidified to pH 3.8, and the resulting acid was lactonized in toluene at 90°C for 8 hr to afford the desired lactone 2 in 86% yield after crystallization (mp. 86-87°,α_D=+39.0°,c=1.0($CHCl_3$))[15].



Thus, we have established an efficent method for the diastereospecific construction of non-racemic β-hydroxy-δ-lactones wherein readily available "chiral synthon" 5 introduces the 3(R)-hydroxyl stereochemistry, which in turn directs the stereospecific reduction of the 5-keto functionality.

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References

1. Total syntheses: Hsu, C.-T.; Wang, N.-Y.; Latimer, L.H.; Sih, C.J. J. Amer. Chem. Soc., 105, 593 (1983). Hirama, M.; Uei, M. Ibid, 104, 4251 (1982). Girotra, N.N.; Wendler, N.L. Tetrahedron Lett., 23, 5501 (1982). Girotra, N.N.; Wendler, N.L. Ibid, 24, 3687 (1983). Grieco, P.A.; Zelle, R.E.; Lis, R.; Finn, J. J. Am. Chem. Soc., 105, 1403 (1983). Synthesis of the β-hydroxy- -lactone: Prugh, J.D.; Deana, A.A.; Tetrahedron Lett., 23, 281 (1982). Yang, Y.-L.; Falck, J.R. Ibid, 23, 4305 (1982). Danishefsky, S.; Kerwin, J.F.; Kobayshi, S. J. Amer. Chem. Soc., 104, 358 (1982). Prasad, K.; Repic, O. Tetrahedron Lett., 25, 2435 (1984). Prasad, K; Repic, O. Ibid, 25, 3391 (1984). Rosen, T.; Taschner, M.J.; Heathcock, C.H. J. Org. Chem., 49, 3994 (1984). Majewski, M.; Clive, D.L.J.; Anderson, P.C. Tetrahedron Lett., 25, 2101 (1984).

2. Total synthesis: Hirama, M.; Iwashita, M. Tetrahedron Lett., 24, 1811 (1983).

3. Analog syntheses: Lee, T.-J.; Holtz, W.J.; Smith, R.L. J. Org. Chem., 47, 4750 (1982). Kuo, C.H.; Patchett, A.A.; Wendler, N.L. Ibid, 48, 1991 (1983). Yang, Y.-L. Manna, S.; Falck, J.R. J. Amer. Chem. Soc., 106, 3811 (1984). Falck, J.R.; Yang, Y.-L. Tetrahedron Lett., 25, 3563 (1984).

4. Willard, A.K.; Novello, F.C.; Hoffman, W.F.; Cragoe, E.J.; U.S. Patent, 1983, 4,375,475; the genesis and biological activity of 2 will be published elsewhere.

5. Bock, K.; Lundt, I.; Pedersen, C. Acta. Chem. Scand., B, 37, 341 (1983). Isbell, H.S., Frush, H.L. Carbohyd. Res., 72, 301 (1979).

6. The 3(S)-hydroxyl stereochemistry of 13a derives directly from the C5(R)-hydroxyl group of isoascorbic acid.

7. (a) Narasaka, K.; Pai, F.C., Tetrahedron 40, 2233 (1984). (b) The use of methanol in our modified Narasaka procedure was found to increase the rate of reduction without decreasing the reaction specificity.

8. C.S. Rondestvedt, Jr. Org. Reactions, 24, 225 (1977).

9. Organozinc compound 9 was prepared from commercially available 5-bromo-2-fluorotoluene by initial conversion to the corresponding Grignard reagent with 1.05 equiv of magnesium in tetrahydrofuran followed by the addition of 0.56 equiv of anhydrous zinc chloride.

10. Negishi, E.; King, A.O.; Okukado N. J. Org. Chem., 42, 1821 (1977).

11. Arseniyadis, S.; Kyler, K.S.; Watt, D.S. Org. Reactions, 31, 1 (1984).

12. The major by-product of the reaction was starting material cyanohydrin 12b resulting from protonation of acyl anion under the reaction conditions. Starting material 12b was also isolated in 25-30% yield.

13. The enantiomeric excess of diol 16 was >98% and relates directly to the ee of iodo ester 14 as obtained from isoascorbic acid.

14. The ratio of syn diol 16 to its anti diastereomer was 100:1. Enantiomeric and diastereomeric purity of 16 was obtained by conversion to the corresponding R(+)-α-methylbenzylamides (10 equivalents of 99.9+% pure R(+)-α-methylbenzylamine at 90° for 12 hr) and HPLC separation on Dupont Zorbax silica gel eluting with hexane: diethyl ether: methyl t-butyl ether: acetic acid (4:3:6:1).

15. Satisfactory infrared and proton magnetic resonance spectra were obtained for all compounds. Satsifactory CHFN analysis was obtained for compounds 2,7,8,10,11 and 16.

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