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SYNTHETIC STUDIES RELATED TO COMPACTIN AND MEVINOLIN: A NEW SYNTHESIS OF THE LACTONE SYSTEM.

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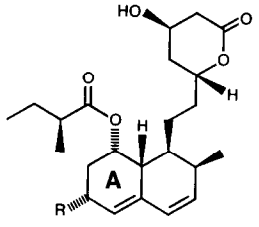
SUMMARY: (S)-Malic acid diethyl ester was converted into a precursor of the lactonic portion of compactin and mevinolin. The substance was coupled with benzyl p-tolyl sulfone and elaborated into the chiral lactone system of the natural products.

Compactin (1, R = H) and mevinolin (1, R = Me) are fungal metabolites that reduce blood levels of cholesterol in man.[1] The important implications for treatment of coronary artery disease have made these compounds the subject of intense research aimed at biological evaluation, chemical synthesis,[2] and modification of the natural products.[3] A flexible synthesis that can lead easily to analogues, particularly[4] those varying in the substitution pattern of ring A, could be a useful contribution to the subject. As part of our research[5a] in this area, we report a new way of making the lactone ring system in the correct optically active form.[6]



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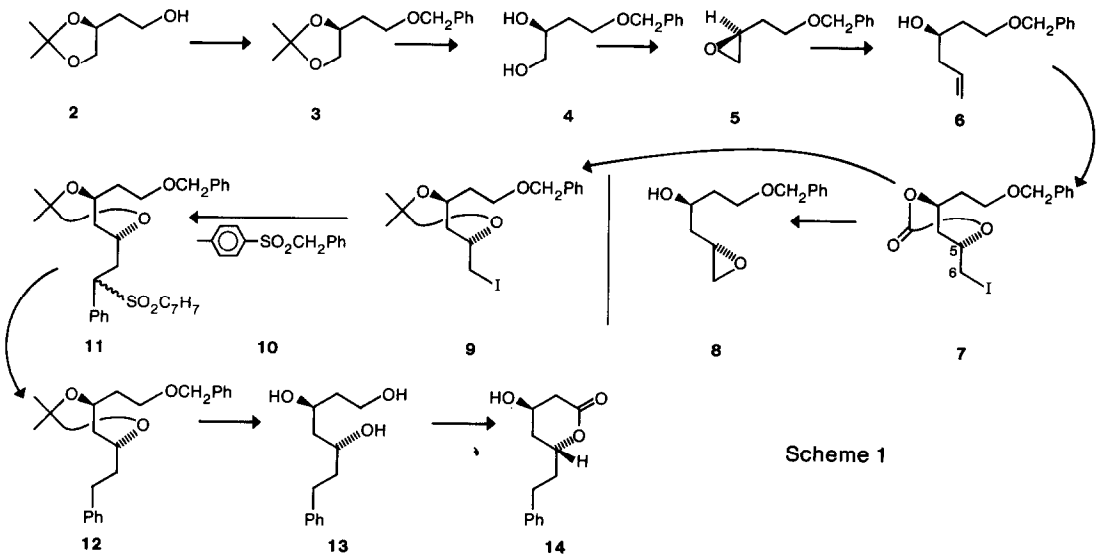
(S)-Malic acid diethyl ester[7] was converted by a short published method[8] into the protected triol 2 (31% from diester). Benzylation (NaH, DMF, $PhCH_2Br$, 0°C, 2 H, then room temp., 20 h) gave (Scheme 1) the ether 3[9] (91%) and hydrolysis (3 → 4,[9] 95%) [AcOH—H_2O (3 : 1), 50°C, 1 h] followed by mesylation (MsCl, pyridine, -60°C, 2 h, then room temp., 20 h) and treatment with Triton B in ether (room temp., 1 h) generated the chiral epoxide 5 [65% from 4; $[\alpha]_D^{26}$ -13.4° (c = 0.39 M, EtOH)]. This substance is properly constituted for introduction of the second chiral centre [C(5) in 7] and of an electrophilic centre [C(6) in 7] which is needed for coupling to another carbon unit.

Epoxide 5 was converted (92%) into alcohol 6 by the action of vinyl magnesium bromide[10] (THF, room temp., 12 h). Deprotonation (hexane—BuLi, THF, 0°C,

10 min.) and treatment first with CO_2 (room temp., 30 min.) and then with I_2 (3 mol. equiv., 0°C, 2 h, room temp., 30 min.) transformed[11] 6 into the (3*S*,5*S*)-iodocarbonate 7 (69%). The material was contaminated by a small amount [<10%, ^{1}H NMR (400 MHz)] of its (3*S*,4*R*)-isomer. Exposure to K_2CO_3 (3 mol. equiv., room temp., 1.5 h) in MeOH gave (74%) epoxide 8, also as an isomer mixture. However,



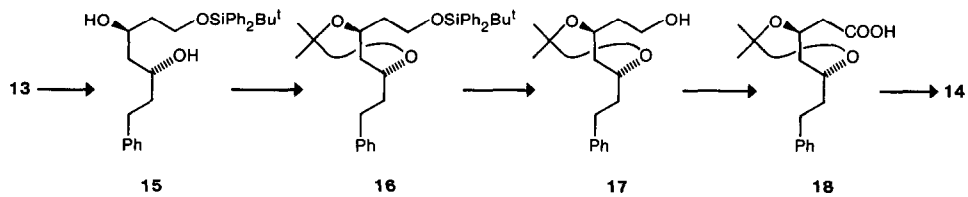
Scheme 1

hydrolysis of 7 and concomitant ketalization (acetone, $TsOH \cdot H_2O$, reflux, 4 h, then room temp., 12 h) followed by chromatography led to isomerically pure ketal 9 (63%). This substance[12] was coupled with the model sulfone 10 (ca. 89%; KH, DMF, room temp., 3 h) and the lactone ring was elaborated in the following way.

Desulfonation of 11[13] [78% overall from 9 without purification of 11; 6% Na(Hg), MeOH, 0°C, 2 h, room temp., 12 h] and deprotection of the product 12 with Me_3SiI (30 min., room temp.) gave the triol 13 (73%, or 94% with one recycling of recovered 12) which could be converted directly (20%) with Fetizon's reagent into the model lactone 14 {$[\alpha]_D^{24}$ +48.8 (c = 0.20 M, $CHCl_3$)}. This compound represents the top portion of compactin and mevinolin. A more efficient synthesis (33% from 13 vs. 20%) was achieved in the manner summarized by Scheme 2.

Partial silylation (13 → 15, t-$BuPh_2SiCl$, DMF, imidazole, room temp., 4 h) and ketalization (15 → 16, acetone, trace $TsOH \cdot H_2O$, room temp., 2 h), without purification of the intermediate 15, gave 16 (53% overall from 13) from which the silicon protecting group was removed (96%; $Bu_4N^+F^-$, THF, room temp., 2.5 h). Oxidation of alcohol 17, first with Collins reagent in dichloromethane (room temp., 1 h) and then with PDC in DMF (room temp., 20 h) followed by hydrolysis of the resulting acetonide (CH_2Cl_2, a few drops conc. HCl, room temp., 2 h)[14] gave lactone 14 (66%).

Alcohol 17 was also obtained directly from 12 (68%, or 97% when corrected for recovered 12) by hydrogenolysis (H_2, 10% Pd—C, EtOH, trace AcOH). The route



Scheme 2

via 15 and 16 was developed because it is expected to be compatible with the presence of double bonds when applied to the actual natural product synthesis.

In summary, the above experiments represent a new way of generating the optically pure (*R*,*R*) lactone unit of compactin and mevinolin and they also serve to illustrate coupling of a synthon for this unit to a model used to represent the bottom portion of the natural products.[15]

All new compounds were fully characterized and had satisfactory mass measurement and/or combustion analysis values.

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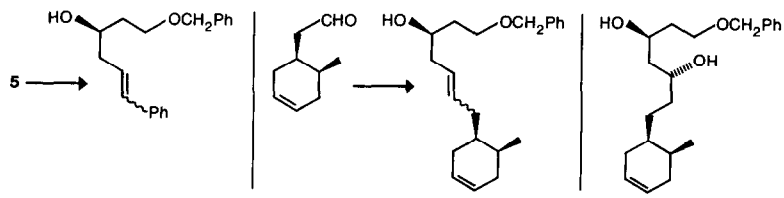
References

1. E.g., Tolbert, J.A.; Bell, G.D.; Birtwell, J.; James, I.; Kubovetz, W.R.; Pryor, J.S.; Buntinx, A.; Holmes, I.B.; Chao, Y.-S.; Bolognese, J.A. J. Clin. Invest., 1982, 69, 913.
2. (a) Hsu, C.-T.; Wang, N.-Y.; Latimer, L.H.; Sih, C.J. J. Am. Chem. Soc., 1983, 105, 593; (b) Hirama, M.; Uei, M. J. Am. Chem. Soc., 1982, 104, 4251; (c) Grieco, P.A.; Zelle, R.E.; Lis, R.; Finn, J. J. Am. Chem. Soc., 1983, 105, 1403; (d) Girotra, N.N.; Wendler, N.L. Tetrahedron Lett., 1983, 3687; (e) Hirama, M.; Iwashita, M. Tetrahedron Lett., 1983, 1811; (f) Funk, R.L.; Zeller, W.E. "Abstract of Papers," 186th National Meeting of the American Chemical Society, Washington, D.C., August 1983; ORGN 7.
3. (a) Endo, A.; Kuroda, M.; Tanzawa, K. FEBS Lett., 1976, 72, 323; (b) Willard, A.K.; Smith, R.L. J. Labelled Compd. Radiopharm., 1982, 19, 337; (c) Lee, T.-J.; Holtz, W.J.; Smith, R.L. J. Org. Chem., 1982, 47, 4750; (d) Kuo, C.H.; Patchett, A.A.; Wendler, N.L. J. Org. Chem., 1983, 48, 1991.
4. E.g., Mevinolin (1, R = Me) is more active than Compactin (1, R = H): Alberts, A.W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. Proc. Natl. Acad. Sci. USA, 1980, 77, 3957.
5. (a) Anderson, P.C.; Clive, D.L.J.; Evans, C.F. Tetrahedron Lett., 1983, 1373. For related work see: (b) Funk, R.L.; Zeller, W.E. J. Org. Chem., 1982, 47, 180; (c) Deutsch, E.A.; Snider, B.B. J. Org. Chem., 1982, 47, 2682; (d) Deutsch, E.A.; Snider, B.B. Tetrahedron Lett., 1983, 3701; (e) Heathcock, C.H.; Taschner, M.J.; Rosen, T.; Thomas, J.A.; Hadley, C.R.; Popják, G. Tetrahedron Lett., 1982, 4747.
6. (a) Yang, Y.-L.; Falck, J.R. Tetrahedron Lett., 1982, 4305; (b) Wareing, J. R.; Fuller, C.E.; Kathawala, F.G. "Abstract of Papers," 185th National Meeting of the American Chemical Society, Seattle, Washington, March 1983, ORGN 11; (c) Prugh, J.D.; Deana, A.A. Tetrahedron Lett., 1982, 281; (d) Danishefsky, S.; Kobayashi, S.; Kerwin, J.F. Jr. J. Org. Chem., 1982, 47, 1981; (e) Heathcock, C.H.; Taschner, M.J.; Thomas, J.A. "Abstract of Papers," 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1982, ORGN 13.

7. Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N.P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmitt, M. Helv. Chim. Acta, 1977, 60, 301.
8. (a) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. J. Am. Chem. Soc., 1973, 95, 8749; (b) Meyers, A.I.; Lawson, J.P. Tetrahedron Lett., 1982, 4883 and references therein.
9. Cf. Tang, K.-C.; Tropp, B.E.; Engel, R. Tetrahedron, 1978, 34, 2873.
10. Vinyl lithium did not react in the required sense.
11. (a) Bongini, A.; Cardillo, G.; Orena, M.; Prozi, G.; Sandri, S. J. Org. Chem., 1982, 47, 4626; (b) Bartlett, P.A.; Meadows, J.D.; Brown, E.G.; Morimoto, A.; Jernstedt, K.K. J. Org. Chem., 1982, 47, 4013.
12. Epoxide 8, after protection (80%; dihydropyran, PPTS, CH_2Cl_2, room temp., 20 h) was also coupled with the sulfone (71%; NaH, DMF, room temp., 4 h).
13. Trost, B.M.; Arndt, H.C.; Strege, P.E.; Verhoeven, T.R. Tetrahedron Lett., 1976, 3477. Compound 11 was difficult to separate from traces of impurities.
14. Girotra, N.N.; Wendler, N.L. Tetrahedron Lett., 1982, 5501.
15. Epoxide 5, on treatment with $Ph_3P{=}CH^{\ominus}$ (ref. 16) and then with benzaldehyde gave 19 (50%). Similarly, racemic aldehyde 20 (ref. 17) was converted into 21 (26%), a substance that is a potential precursor (cf. 6 → 7) of 22.
16. Corey, E.J.; Kang, J. J. Am. Chem. Soc., 1982, 104, 4724.
17. Prepared via homologation [MeSC⁻HS(O)Me] of the corresponding racemic norbromide: Unpublished observations.



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