Tetrahedron Letters, Vol. 34, No. 1, pp. 39-42, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

Phosphorus-Containing Inhibitors of HMG-CoA Reductase. 3. Synthesis of Hydroxyphosphinyl-Analogues of the Mevinic Acids

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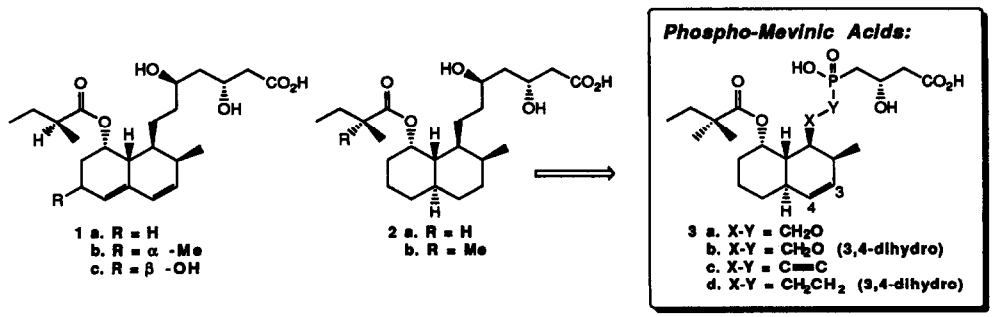
Abstract: *The synthesis of a series of hydroxyphosphinyl-containing analogues of the HMG-CoA reductase inhibitor trans-tetrahydrocompactin is described.*

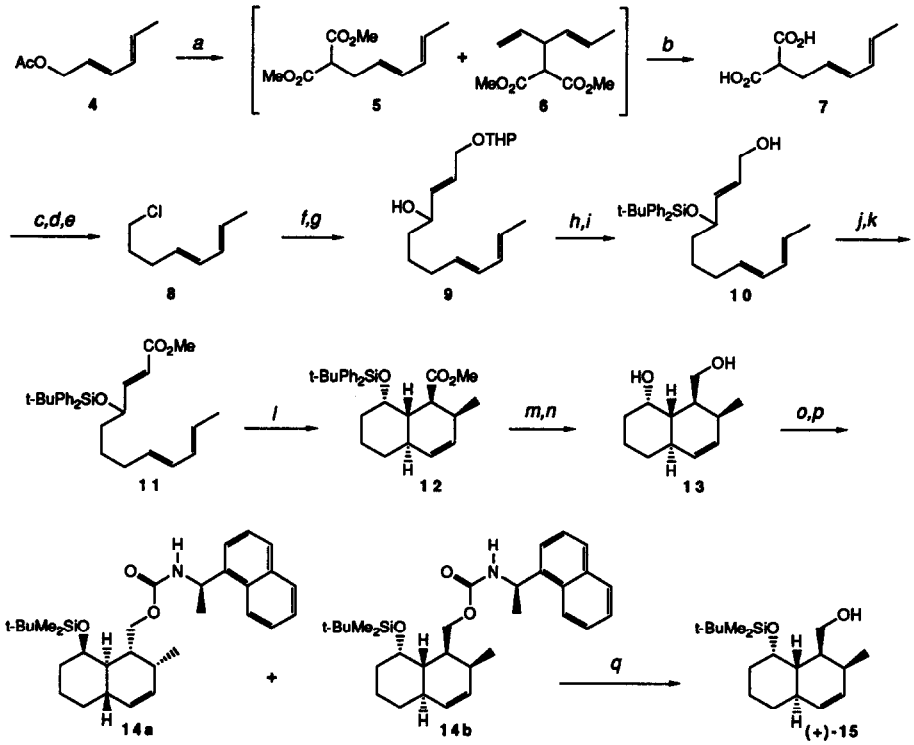
Several members of the mevinic acid family of HMG-CoA reductase inhibitors (e.g., **1a-c**) have now been shown to be effective in lowering plasma cholesterol in a variety of animal models and in humans.[2] Extensive structure-activity studies[3,4ab] on reduced analogues of the mevinic acids (e.g., **2ab**) have demonstrated that the *trans* ring junction stereochemistry as well as the presence of an axial methyl group *cis* to the 3,5-dihydroxyheptanoic acid side chain are crucial for maximal inhibitory activity. We have recently reported[5ab] the rationale for the design and synthesis of a new class of HMG-CoA reductase inhibitors which utilize a hydroxyphosphinyl function in place of the C-5 hydroxyl group found in a diverse group of synthetic reductase inhibitors which incorporate a "biphenyl-like" nucleus in place of the decalin ring system of the mevinic acids. In this paper we extend this concept to a series of hydroxyphosphinyl-containing mevinic acid analogues **3a-d** based on the *trans*-tetrahydrocompactin analogue **2b**.



The hexahydronaphthylene nucleus of our phospho-mevinic acid analogues was assembled in racemic form by a modification of the Diels-Alder strategy originally developed by Funk and Zeller[6ab] for the total synthesis of compactin (see Scheme 1). Although palladium catalyzed alkylation[7] of dimethyl sodiomalonate with sorbyl acetate (**4**) produced a 2.5:1 mixture of diesters **5** and **6** (78% combined yield) the desired diacid **7** (mp 134-135°C) could be easily be obtained free of isomeric impurities in 51% overall yield from **4** by simple recrystallization of the mixture of the corresponding diacids from Et_2O-hexane. In our hands, alkylation of the Grignard reagent derived from chloride **8** with *(E)*-MeO_2C-CH=CH-CHO (-78° to -25°C, THF)[6a] gave a complex mixture of products from which the desired alcohol could be isolated in only 31% yield. However, this problem was easily circumvented by carrying out the Grignard reaction on a substrate

containing a latent ester function. Thus, reaction of the Grignard reagent derived from **8** with *(E)*-THPO-CH_2-CH=CH-CHO[8] gave allylic alcohol **9** in 94% yield.

Scheme 1

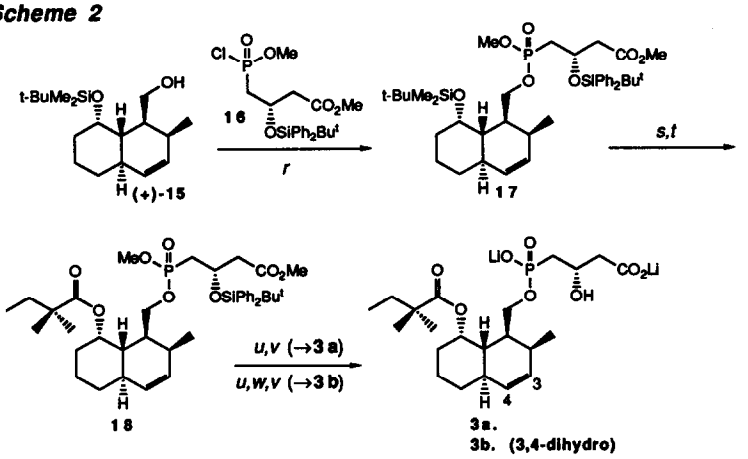


Reagents and Conditions: (a) $NaCH(CO_2Me)_2$, $Pd(PPh_3)_4$, PPh_3, THF, reflux; (b) 4N NaOH, MeOH, reflux; recryst from Et_2O-hexane; (c) CuO, MeCN, reflux; (d) $LiAlH_4$, Et_2O; (e) $SOCl_2$, pyridine, PhH, reflux; (f) Mg, THF, reflux; (g) *(E)*-OHC-CH=CH-CH_2OTHP, THF, -78°C; (h) t-$BuPh_2SiCl$, imidazole, DMAP, DMF; (i) p-TsOH, MeOH; (j) MnO_2, hexane; (k) MnO_2, NaCN, AcOH, MeOH; (l) $EtAlCl_2$, CH_2Cl_2; (m) $LiAlH_4$, THF, reflux; (n) 1.0 M n-Bu_4NF, THF; (o) *R(-)*-1-(1-naphthyl)ethyl isocyanate, pyridine, 60°C; (p) t-$BuMe_2SiCl$, imidazole, DMAP, DMF, 80°C; (q) $LiAlH_4$, THF, reflux.

Lewis acid catalyzed Diels-Alder reaction of **11** following the Funk protocol[6a] gave exclusively the desired endo adduct **12** in 73% yield as a 95:5 mixture of epimers at the silyloxy group. The stereochemistry of the major product was readily apparent from its proton NMR spectrum and is consistent with that reported by Funk[6a] for the corresponding t-butyldimethylsilyl ether. The minor isomer was easily removed by flash chromatography on silica gel after reduction of the methyl ester with $LiAlH_4$. Treatment of diol **13** with *(R)*-1-(1-naphthyl)ethyl isocyanate in pyridine (60°C, 3.5 hrs) followed by silylation with t-butyldimethylsilyl chloride gave a diastereomeric mixture of urethanes[9] which were readily separated by flash chromatography on silica gel to give **14a** and **14b** in 44% and 41% overall yields, respectively from diol **13**. Reductive cleavage of the separated urethanes with $LiAlH_4$ (94-96% yield) afforded the enantiomeric decalins (e.g., **15**) with essentially equal and opposite rotations.[10]

Condensation of (+)-**15**[11] with phosphonochloridate **16**[5a] in CH_2Cl_2-pyridine gave the mixed diester **17** in 85% yield. Selective cleavage of the t-butyldimethylsilyl ether of **17** with aqueous HF in acetonitrile (67%, 89% corrected for recovered **17**) followed by esterification of the resulting secondary, axial alcohol with 2,2-dimethylbutyryl chloride gave ester **18** (78% yield). Cleavage of the remaining silyl ether with n-BuN_4F-AcOH in THF and hydrolysis of the carboxylic and phosphonic methyl esters proceeded smoothly to afford the target phosphonic monoester **3a** in excellent overall yield. Similarly, hydrogenation of the desilylated intermediate over Pt-C followed by basic hydrolysis afforded the corresponding 3,4-dihydro analogue **3b**.

Scheme 2



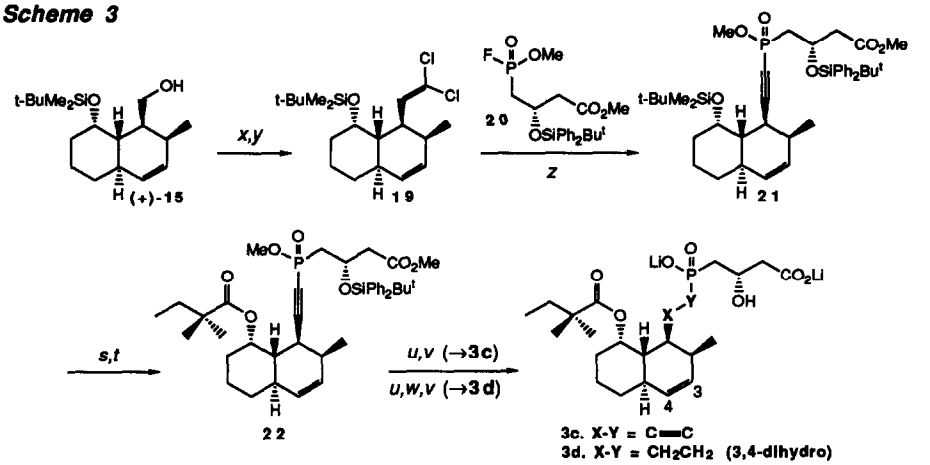
Reagents and Conditions: (r) **16** in CH_2Cl_2 added dropwise to (+)-**15** in pyridine; (s) 48% HF, MeCN; (t) 2,2-dimethylbutyryl chloride, DMAP, pyridine, 80°C; (u) n-Bu_4NF (3 equiv), AcOH (4 equiv), THF; (v) 1.0 N LiOH, dioxane, 50°C; (w) H_2, 10% Pt-C, MeOH.

Oxidation of (+)-**15** with tetra-n-propylammonium perruthenate/NMO[12] followed by treatment of the resulting unstable aldehyde with $BrCCl_3$-PPh_3 in acetonitrile[13] gave dichloro-olefin **19** in 76-85% overall yield. The acetylenic anion generated *in situ* by treatment of **19** with 2.1 equivalents of n-BuLi in THF at -78°C was quenched with phosphonofluoridate **20**[14] to give acetylenic phosphinate **21** in 89% yield. Selective cleavage of the t-butyldimethylsilyl ether of **21** and esterification of the resulting alcohol was accomplished using the methodology described above for the phosphonate-based inhibitors. Direct deprotection following the usual protocol afforded the acetylenic phosphinic acid **3c**. The reduced analog **3d** was prepared by hydrogenation of the intermediate alcohol over Pt-C followed by basic hydroylsis of methyl esters.

Compared to its dihydroxy isostere **2b** (I_{50} = 93 nM), phosphinic acid **3d** (I_{50} = 4.9 nM) was nearly 20-fold more potent as an inhibitor of rat microsomal HMG-CoA reductase[15]. While phosphonate **3b** (I_{50} = 290 nM) was 57X less active than its carbon isotere **3d**, its potency was significantly enhanced by the introduction of a double bond in the "A-ring" of the decalin nucleus (i.e., **3a**, I_{50} = 20 nM). In contrast, acetylenic phosphinic acid **3c** (I_{50} = 2,300 nM) was a relatively poor inhibitor of reductase. This study

demonstrates that the replacement of the C-5 hydroxyl of the mevinic acids by a hydroxyphosphinyl function can lead to enhanced binding to the active site of HMG-CoA reductase.

Scheme 3



Reagents and Conditions: (x) TPAP, NMO, 4Å molecular sieves, CH_2Cl_2; (y) $BrCCl_3$, Ph_3P, MeCN; (z) **19** in THF treated with n-BuLi/hexane (2.05 equiv) at -78°C; after 1 hr at -78°C added to **20** in THF at -78°C; (s) 48% HF, MeCN; (t) 2,2-dimethylbutyryl chloride, DMAP, pyridine, 80°C; (u) n-Bu_4NF (3 equiv), AcOH (4 equiv), THF; (v) 1.0 N LiOH, dioxane, 50°C; (w) H_2, 10% Pt-C, MeOH.

References and Notes

1. (a) Present address: Glaxo Inc. Research Institute, Five Moore Dr., Research Triangle Park, NC 27709 (b) present address: Vertex Pharmaceuticals, 40 Allston St., Cambridge MA 02139-4211.
2. Hoeg, J. M.; Brewer, H. B. *J. Am. Med. Assoc.* **1987**, *258*, 3532.
3. (a) Endo, A. *J. Med. Chem.* **1985**, *28*, 401. (b) Lee, T.-J. *TIPS* **1987**, *8*, 442. (c) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849. (d) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991. (e) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750.
4. (a) Karanewsky, D.S. *Tetrahedron Lett.* **1991**, *32*,3911. (b) Patel, D. V.; Gordon, E. M. *Biorg. and Med. Chem. Lett.* **1991**, *1*, 509.
5. (a) Karanewsky, D. S.; Badia, M. C.; Ciosek, C. P.; Robl, J. A.; Sofia, M. J.; Simpkins, L. M.; DeLange, B.; Harrity, T. W.; Biller, S. A.; Gordon, E. M. *J. Med. Chem.* **1990**, *33*, 2952. (b) Robl, J. A.; Duncan, L. A.; Pluscec, J.; Karanewsky, D. S.; Gordon, E. M.; Ciosek, C. P.; Rich, L. C.; Dehmel, V. C.; Slusarchyk, D. A.; Harrity, T. W.; Obrien, K. A. *J. Med. Chem.* **1991**, *34*, 2804.
6. (a) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180 and (b) Zeller, W. E. Ph.D. Thesis **1988**, U. of Nebraska.
7. Trost, B. M.; Verhoeven, T. R. *J. Amer. Chem. Soc.* **1980**, *102*, 4730.
8. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.
9. TLC (silica gel, EtOAc-toluene; 5:95) **14a**: R_f = 0.43; **14b**: R_f = 0.51.
10. All new compounds gave spectral data consistent with the assigned structure. Selected mps and optical rotations; **12**: mp 76-77.5°C, **13**: mp 128-129°C; **14a**: $[\alpha]_D$ = -79.4°, c = 0.67, $CHCl_3$; **14b**: $[\alpha]_D$ = +82.0°, c = 0.52, $CHCl_3$; (+)-**15**: mp 71-72°C, $[\alpha]_D$ = +126.1°, c = 0.51, $CHCl_3$; **19**: mp 50-53°C, $[\alpha]_D$ = +133.5°, c = 1.05, hexane; **3a**: $[\alpha]_D$ = +85.3°, c = 0.63, MeOH; **3b**: $[\alpha]_D$ = +47.4°, c = 0.65, MeOH; **3c**: $[\alpha]_D$ = +151.3°, c = 0.55, MeOH; **3d**: $[\alpha]_D$ = +63.6°, c = 0.65, MeOH.
11. Absolute configuration of (+)-**15** was confirmed by conversion (n-Bu_4NF, THF) to diol (+)-**13** ($[\alpha]_D$ = +132.4, c= 0.50, $CHCl_3$) of known absolute configuration (lit. $[\alpha]_D$ = +131°, c = 5.35, $CHCl_3$, see reference 6b).
12. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
13. Burton, G.; Elder, J. S.; Fell, S. C. M.; Stachulski, A. V.; *Tetrahedron Lett.* **1988**, *29*, 3003.
14. Phosphonofluoridate **20** was prepared by treatment of the corresponding phosphonic monomethyl ester (see ref. 5ab) with 1-methyl-2-fluoropyridium toslylate and i-Pr_2NEt in CH_2Cl_2 (rt, 18 hrs), J. Godfrey, unpublished results.

15. The authors wish to thank Dr. Carl P. Ciosek and Dorothy A. Slusarchyk for determination of reductase inhibitory activities of compounds **3a-d**.

(Received in USA 2 September 1992)