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Synthetic Transformations of the Mevinic Acid Nucleus: Preparation of a Monocyclic Analogue of Compactin

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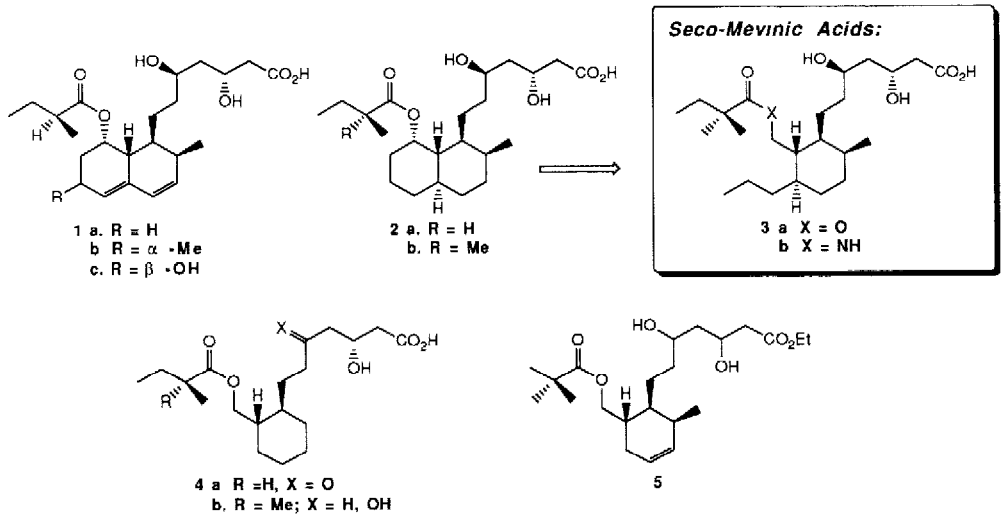
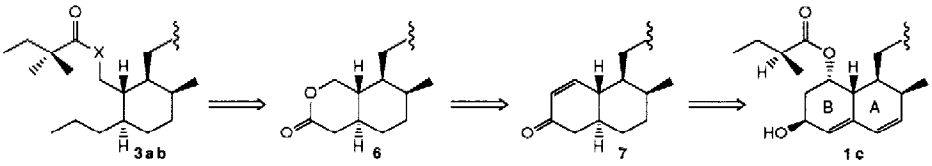
Abstract: *The synthetic transformation of pravastatin into a fully functional, monocyclic analogue of compactin via a multistep sequence is described*

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.[1] Extensive structure-activity studies[2] have suggested that the primary role of the mevinic acid decalin nucleus is to serve as a rigid template for the crucial 3,5-dihydroxyheptanoic acid and α-methylbutyrate side chains. However, there has been no direct support for this hypothesis. Seco-mevinic acid **3a** was targeted because it retains all of the ring carbons of the mevinic acids, and is conceptually the result of breaking the C-C bond adjacent to the butyrate ester of *trans*-tetrahydrocompactin analogue **2a**. In light of the importance of ester side chain in enzyme binding, the corresponding amide isostere **3b** was also of interest. Attempts by other workers at this type of modification have recently appeared in the literature.[3] Heathcock reported[3a] a monocyclic analogue of compactin ketone (i.e., **4a**) which was 10^4 less active than its decalin based counterpart. We have confirmed this result[4] with the structurally analogous dihydroxyheptanoic acid analogue **4b**. Likewise, workers at Sandoz[3b] have reported a similar compound which retains the axial methyl group of the natural products but still shows poor activity against reductase Seco-mevinic acid **3a**



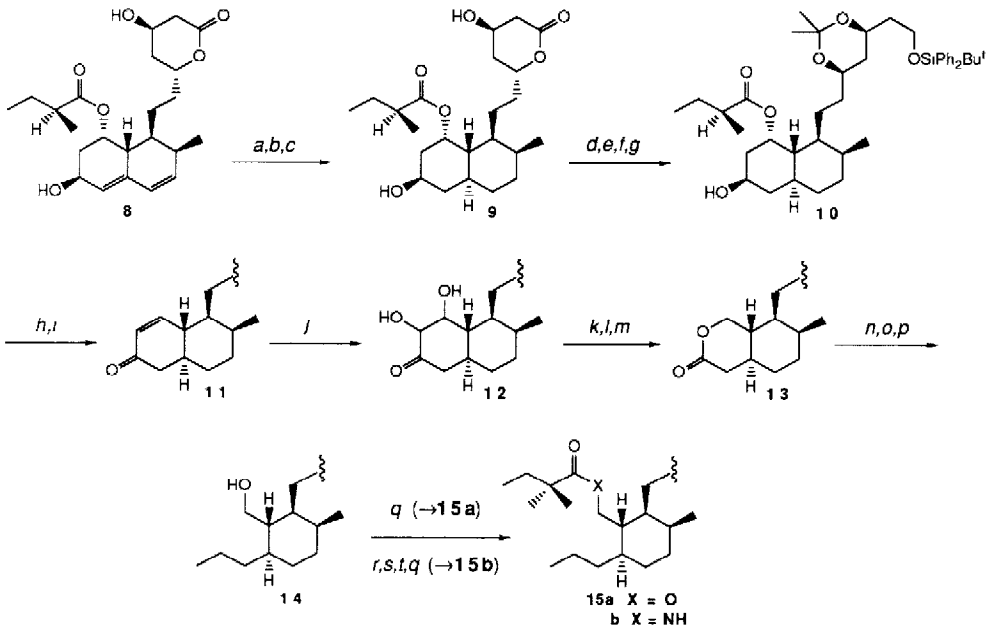
differs from these attempts in that it still bears a stereochemically defined substituent (i.e , n-propyl) at the 3-position of the cyclohexane nucleus.

Retrosynthetic analysis suggested that the four contiguous chiral centers found in the cyclohexane nucleus of **3ab** might be derived from the hexahydronaphthalene nucleus of pravastatin (**1c**). δ-Lactone **6** could serve as a convenient precusor to both the ester and n-propyl side chains of **3a**. Lactone **6** is the product of an oxidative cleavage[5] of the corresponding cyclohexenone **7** This process requires the excision of the α-carbon of the cyclohexenone. Enone **7**, in turn, could be produced by an elimination of the β-acyloxyketone derived from **1c**. In order to protect the labile 3,5-dihydroxyheptanoic acid side chain from β-elimination during these operations, we felt it would be necessary to reduce the acid to the alcohol oxidation state.



With this strategy in mind, **1c** was converted to the corresponding δ-lactone **8**[6] by treatment of the corresponding free acid with TFA in EtOAc Silylation of the 2° allylic hydroxyl was necessary to block the β-face of the decalin system during the hydrogenation of the diene moiety Following this protocol,[7] the *trans*-fused decalin alcohol **9**[8] was obtained in 86% yield after removal of the silyl ether with aq HF in MeCN. Hydrogenation of the corresponding free allylic alcohol **8** under the same conditions produced a 1:1 mixture of *cis* and *trans*-decalins. Reduction of the lactone moiety of **9** in the presence of the α-methylbutyrate was best accomplished by successive reactions with DiBAL-H at -78° and $NaBH_4$ in MeOH-THF. Selective silylation of the resulting tetraol with t-$BuPh_2SiCl$ followed by treatment with p-TsOH in acetone gave the silyl ether-acetonide **10** in 62% overall yield for 4 steps. The stage was now set for the modification of the "B-ring" of the decalin nucleus Oxidation of the remaining 2° alcohol with Dess-Martin periodinane[9] followed by treatment of the resulting β-acyloxyketone with DBU in toluene gave the cyclohexenone **11** in 95% yield. Ozonolysis of the enone followed by reductive workup with $NaBH_4$ following the Heathcock procedure[5a] failed to produce the desired δ-lactone **13**. However, the same transformation could be achieved in high overall yield utilizing a modification of the Danishefsky[5b] methodology. Osmylation of the enone gave the corresponding keto-diol **12** as a mixture of α- and β-isomers which were reacted sequentially with $NaIO_4$, CH_2N_2 and $Li(OBu^t)_3AlH$ to afford the desired δ-lactone **13** in 80% overall yield from enone **11** DiBAL-H reduction of lactone **13** followed treatment of the resulting lactol with methylene triphenylphosphorane gave a δ-hydroxy olefin which, in turn, was hydrogenated over Pd-C to give alcohol **14** in 92% overall yield Esterification with 2,2-dimethylbutyryl chloride (**14**→**15a**) completed the transformation of the "B-ring" of pravastatin to the desired acyloxymethyl and alkyl side chains of **3a**. For the synthesis of the amide isostere **3b**, alcohol **14** was converted into the corresponding azide via its mesylate in 91% yield. Catalytic reduction of the azide followed by acylation with 2,2-dimethylbutyryl chloride gave the acylaminomethyl derivative **15b** in 76% overall yield.

Scheme 1



Reagents and Conditions: (a) t-BuMe$_2$SiCl (1 05 equiv), DMAP, imidazole, THF; (b) H_2, 10% Pt-C, EtOAc; (c) 48% aq. HF (2 7 equiv), MeCN, (d) DIBAL-H (3.3 equiv), PhMe-THF, -78°C, (e) $NaBH_4$, MeOH-THF (1 4); (f) t-BuPh$_2$SiCl (1.15 equiv), imidazole, DMF, (g) acetone, p-TsOH, (h) Dess-Martin periodinane, t-BuOH, CH_2Cl_2, (i) DBU, PhMe, (j) OsO_4, pyridine; aq $NaHSO_3$; (k) $NaIO_4$, dioxane-H_2O (3 1), (l) CH_2N_2, Et_2O, 0°C; (m) LiAl(OBu^t)$_3$H, THF, 0°C, (n) DIBAL-H, PhMe, -78°C; (o) MePPh$_3$Br, KHMDS, PhMe, (p) H_2, 10% Pd-C, MeOH; (q) 2,2-dimethylbutyryl chloride, DMAP, pyridine; (r) MsCl, Et_3N, CH_2Cl_2, 0°C; (s) NaN_3 (5 equiv), DMF, 50°C; (t) H_2, 10% Pd-C, Et_3N (0 75 equiv), MeOH-EtOH (3.4).

With this phase of the synthesis complete, we next turned our attention to the reconstruction of the 3,5-dihydroxyheptanoic acid side chain. Removal of the t-BuPh2Si-ether of **15ab** unmasked the 1° alcohol which was adjusted to the carboxylic acid oxidation state by sequential treatment with Dess-Martin periodinane and KMnO4 under the Masamune conditions [10] Methyl esters **16ab** were isolated in 77-78% overall yield after treatment of the crude acids with CH_2N_2. Removal of the acetonide protecting groups of **16ab** was best effected by treatment with aq HF-MeCN. Under these conditions, the initially formed ester-diol undergoes rapid lactonization to give the lactones **17ab** in 91-95% yields. Other conditions such as TsOH-MeOH, 1N HCl-THF or AcOH-H_2O gave mixtures of the lactone and the corresponding ester-diol. Finally hydroylsis of the lactones **17ab** with 0.1N LiOH in dioxane gave the desired seco-mevinic acids **3ab**.

In contrast to the previously reported cyclohexane-based inhibitors **4ab** and **5**, **3a** was 12X more potent than its decalin based counterpart **2b** (see Table 1). These results indicate that the butyrate ester need not be conformationally restricted in order to achieve optimal potency with these inhibitors. Compared to the cyclohexane analogue **4b** which contains all of the functional groups but lacks the axial methyl and n-propyl side chains, **3a** is 658X more active. The amide derivative **3b** was about 10-fold less active than its oxygen

isostere **3a** making it about as potent as the decalin-based compound **2b**. The total synthesis of several structurally related seco-mevinic acid analogues will be reported in future publications.

Scheme 2

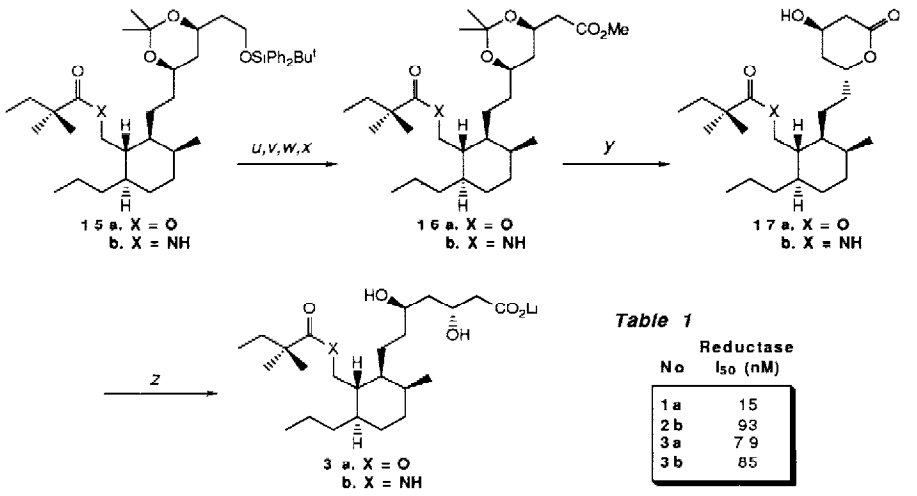


Table 1

No	Reductase I_{50} (nM)
1a	15
2b	93
3a	7 9
3b	85

Reagents and Conditions: (u) n-Bu_4NF, THF, (v) Dess-Martin periodinane, t-BuOH, CH_2Cl_2; (w) 1 0M aq $KMnO_4$, 5% NaH_2PO_4, t-BuOH, (x) CH_2N_2, Et_2O, 0°C, (y) 48% aq HF (6 equiv), MeCN, (z) 0 1N LiOH, dioxane.

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References and Notes

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2. (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. These studies have shown that the diene moiety of the mevinic acids can be reduced with only a slight decrease in inhibitory potency as long as the *trans*-ring junction stereochemisty is maintained (e g , **2a**), the corresponding *cis*-fused tetrahydro-mevinic acids were significantly less active. The crucial α-methylbutyrate ester can also be substituted by an additional methyl group (e.g , **2b**) with essentially no effect on inhibitory activity
3 (a) Heathcock, C H.; Davis, B. R ; Hadley, C R. *J Med Chem* **1989**, *32*,197 (b) Damon, R E , Coppola, G M., Vedananda, T *200th National ACS Meeting*, August 26-31, 1990, Washington, DC.
4 Compound **4b** was prepared by a route analogous to that utilized by Heathcock for the synthesis of **4a**. D. R. Magnin, unpublished results.
5 For examples of cyclohexenone to δ-lactone conversion, see (a) Heathcock, C. H.; Chavdarian, C. G. *J Org Chem* **1975**, *40*, 2970 and (b) Danishefsky, S ; Schuda, P F., Kitahara, T , Etheredge, S J *J Am Chem Soc* **1977**, *99*, 6066 and references therein
6. All new compounds gave spectral and analytical data consistent with the assigned structure Selected mp and optical rotation data, **8** mp 143-144°C, $[\alpha]_D$ = +199 7° (c = 0 59, $CHCl_3$); **9** mp 156-157°C, $[\alpha]_D$ = +75 9° (c = 0.64, $CHCl_3$); **17a**, mp 128-129.5°C, $[\alpha]_D$ = +34 9° (c = 0.54, $CHCl_3$), **17b**: $[\alpha]_D$ = +25 7° (c = 0 54, $CHCl_3$), **8**: $[\alpha]_D$ = +12.1° (c = 0 54, MeOH); **8** $[\alpha]_D$ = +13 8° (c = 0.49, MeOH)
7 The stereoselective hydrogenation of **8** was developed by Dr. J Saunders in our laboratories
8 The structure of **9** was established by single crystal X-ray crystallography. D. S. Karanewsky, M F Malley and J. Z. Gougoutas, unpublished results.
9 Dess, D. B ; Martin, J. C. *J. Org. Chem* **1983**, *48*, 4155
10. Abiko, A ; Roberts, J C , Takemasa, T , Masamune, S *Tetrahedron Lett* **1986**, *27*, 4537

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