Bioorganic & Medicinal Chemistry Letters, Vol.1, No.10, pp. 509-512, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

C-2 Desmethyl Seco-Mevinic Acids. Monocyclic HMG-CoA Reductase Inhibitors

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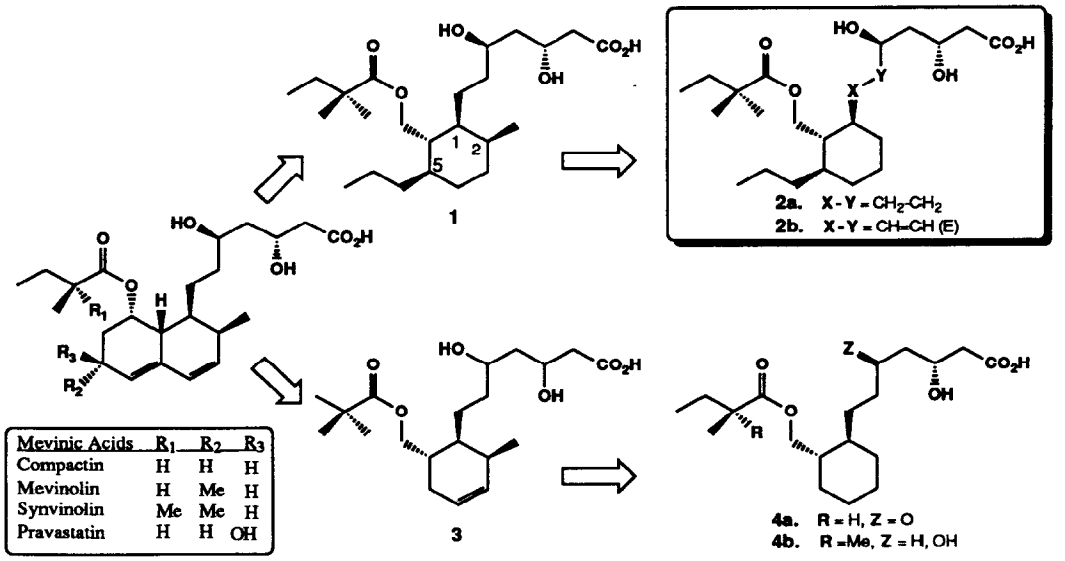
(*Received* 22 *August* 1991)

Abstract: An efficient preparation of C-2 desmethyl seco-mevinic acid **2a** from 2-cyclohexen-1-one (10 steps, 24.7% overall yield) is described. Comparison of the activity of analogs **2a,b** with other recently reported seco-mevinic acid based HMG-CoA reductase inhibitors suggests that all four substituents around the cyclohexyl ring are required for good biological activity.

HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors like pravastatin and lovastatin have recently attracted a great deal of medical attention as cholesterol lowering agents.[1] In our research program directed towards the preparation of potent and selective inhibitors of this enzyme, seco-mevinic acid **1** was recently identified as a novel lead (I_{50} = 8 nM).[2] Unfortunately, the high level of synthetic complexity associated with the preparation of enzyme inhibitors like **1** hindered their rapid exploitation. This prompted us to design a short and practical synthesis of the desmethyl analog **2a**, which if active, would offer greater synthetic flexibility in terms of exploring this new structural class of inhibitors. Herein, we report the synthesis of seco-mevinic acid **2a** and its unsaturated analog **2b**, and by comparing their *in vitro* potency with related seco analogs **3**[3] and **4**[4,5], propose the minimal structural requirements for potent, seco-mevinic acid based HMG-CoA reductase inhibitors.



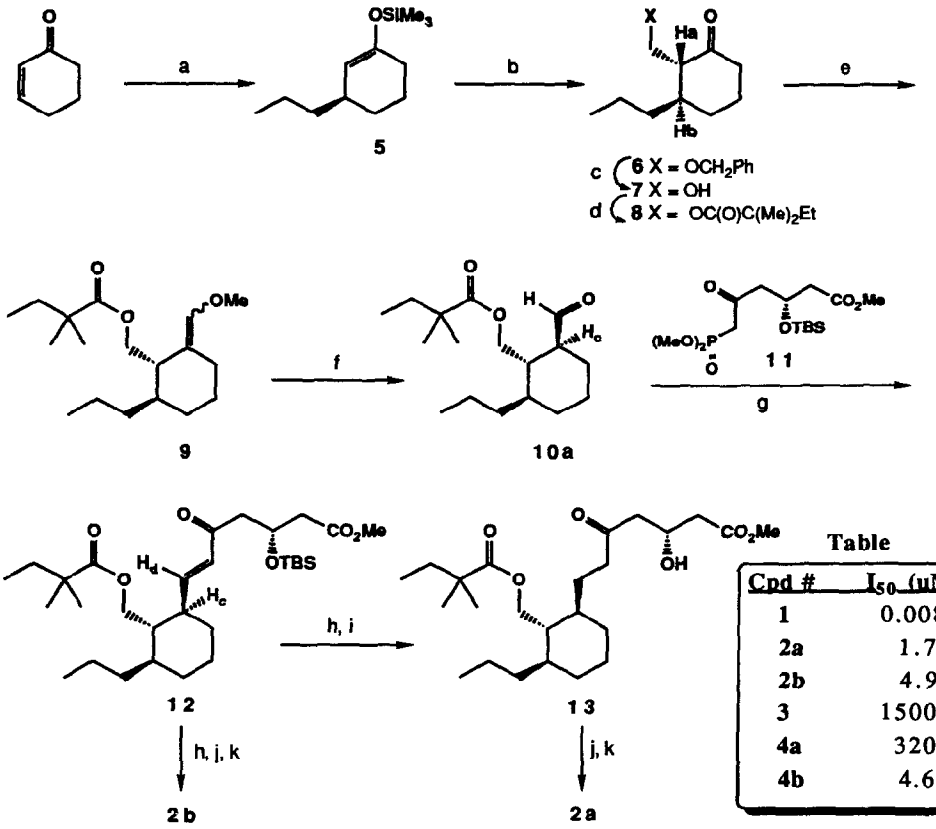
Mevinic Acids	R_1	R_2	R_3
Compactin	H	H	H
Mevinolin	H	Me	H
Synvinolin	Me	Me	H
Pravastatin	H	H	OH

Seco-mevinic acids **2a,b** possesses three contigious chiral centers around the cyclohexane ring, which i turn bear a 1,2-*trans* relationship relative to each other. The most appealing synthetic strategy involved preparatio of aldehyde **10a** and its reaction with the β-ketophosphonate **11**.[6] Since all three substituents in aldehyde **10a** ar equatorial, we envisioned preparing this thermodynamic isomer by Wittig homologation of ketone **6** or **8** followe by epimerization under equilibrating conditions. We planned to secure the 1,2-*trans* relationship in ketone **6** by 1,4-cuprate type addition to cyclohexenone.

Selective 1,4-addition of the n-propyl group to 2-cyclohexen-1-one required considerable experimentatio The copper catalyzed n-propyl Grignard addition proceeded better in ether than in THF. Superior yields wer realized when the enolate was trapped with TMSCl (88%), instead of performing a direct hydrolytic quenc (66%). This highlights the role of chlorotrimethylsilane in enhancing the rate and selectivity of 1,4-additio reactions.[7] While the lithium enolate generated from the silyl enol ether **5** failed to react with benzyl chloromethy ether (BOM-Cl) even in the presence of HMPA or upon addition of NaI, it reacted efficiently with benzy bromomethyl ether (BOM-Br) to provide the β-benzyloxy ketone **6** in high yields. This was a sensitive reactio which gave slightly variable yields (85-94%), but more importantly, its stereoselectivity (>19:1 to 5:1) wa critically dependent on the reaction temperature and the quality of the BOM-Br reagent.[8] Although the minor *ci* epimer could not be removed at this stage, the desired *trans* stereochemistry of the predominant diastereomer was confirmed by ^{1}H NMR (J_{Ha-Hb} = 10.1 Hz). Debenzylation of **6** provided the β-hydroxy ketone **7** and at thi stage, its epimeric contaminant was readily removed by flash chromatography. Acylation of **7** to the ester **8** wa straightforward. In the key event, Wittig homologation of ketone **8** and acidic hydrolysis of the intermediate eno ether **9** worked extremely well to provide the desired aldehyde **10ab** as a separable mixture of epimers in 80% overall yield (73% yield of desired epimer **10a** from **8**).[9] Condensation of racemic aldehyde **10a** with the chira ß-keto phosphonate **11**[6] (LiCl, DBU, CH_3CN)[10] afforded the desired enone **12** in 59% isolated yield (90% conversion), which was accompanied by about 5% of undesired epimer.[11] This reaction thus permitted assembl of entire carbon framework of the final target molecule. In an attempt to minimize epimerization, milder condition recently highlighted by Heathcock (LiBr, Et_3N, CH_3CN) were employed,[4] however, some epimerization wa still observed and the yields and conversion rates proved slightly inferior (32% isolated yield, 56% conversion 5% epimerization). Attempted selective 1,4-reduction of the α,β-unsaturated ketone **12** ($(Ph_3P)_3RhCl$ $PhMe_2SiH$, C_6H_6)[12] followed by hydrolysis with aqueous hydrofluoric acid gave the desired ketone **13**, alon with some related inseparable enone, signifying incomplete reaction during the hydrosilylation step. Alternatively cleavage of the silyl ether group from **12** followed by hydrogenation in ethyl acetate gave **13** in excellent yields Selective *syn* reduction of the ß-hydroxy ketone **13** followed well precedented literature conditions[13] and gave the desired 1,3- diol which, upon hydrolysis with lithium hydroxide and purification by HP20 colum chromatography afforded **2a** as the lithium salt. This completed our preparation of the seco-mevinic acid **2a** from 2-cyclohexen-1-one in 10 steps and 24.7% overall yield. Alternatively, desilylation of **12**, followed by reductio and hydrolysis provided the unsaturated analog **2b**.

The C-2 desmethyl analog **2a** was found to be 212 fold less active as an HMGR inhibitor than the paren compound **1**(see Table). If one of the diastereomers in **2a** is assumed to be inactive,[11a] it still reflects a loss o two orders of magnitude in activity. This suggests that the two substituents on the cyclohexyl ring system tha flank the diol acid side chain might be serving to orient it in the right conformation for optimal binding and/or the

Scheme I



Table

Cpd #	I_{50} (uM)
1	0.008[2]
2a	1.7
2b	4.9
3	1500[3]
4a	320[4]
4b	4.6[5]

a) n-PrMgCl, CuBr.Me_2S, Et_2O; TMSCl, Et_3N, HMPA (88%) b) MeLi, THF, r.t., 45 min.; BOMBr, -78° to r.t. (85-94%) c) H_2, $Pd(OH)_2/C$ (75%) d) $EtC(Me)_2C(O)Cl$, Pyridine, DMAP (95%) e) nBuLi, $Ph_3P^+CH_2OMe\ Cl^-$ f) 4:1 Et_2O/ 35% $HClO_4$, r.t., 14 h (73% **8a** from **6**) g) LiCl, DBU, CH_3CN, r.t., 48 h, (90% conversion, 59% isolated yield) h) 48% aq. HF, CH_3CN (86%) i) H_2, 10% Pd/C, EtOAc (94%) j) Et_3B, $tBuCO_2H$; $NaBH_4$, MeOH; H_2O_2 (84% for **2a**, 75% for **2b**) k) 1N LiOH, dioxane (quant.)

C-2 methyl group is involved in important hydrophobic interactions. While the impressive *in vitro* potency of seco-mevinic acid **1** indicates that conformational restriction of the butyrate ester side chain is not necessary, the inactivity of despropyl analog **3**[3] clearly illustrates the critical requirement of an n-propyl group. The two desalkyl analogs **2a** and **3** involve complementary deletions on the parent acid **1**. However, other structural differences between them precludes a direct accessment of the relative significance of the C-2 vs. C-5 substituents. As expected, further simplification of this class of compounds, represented by **4a**[4] and **4b**[5], has also been found to be ineffective. In conclusion, the results on analogs 2-4 summarized in this communication lead us to hypothesize that **in the monocyclic seco-mevinic acid series, all the four substituents around the cyclohexyl ring are required for efficient binding to and inhibition of HMGR.**

Acknowledgements :

We wish to thank Dr. Carl P. Ciosek for testing of compounds **2a** and **2b**, and Dr. D. S. Karanewsky for helpful discussions during the progress of this work.

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4 Compound **4a**: Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197.

5 Compound **4b** was prepared by Dr. David R. Magnin at Bristol-Myers Squibb (unpublished results).

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8 Utilization of freshly prepared BOM-Br obtained by treatment of benzyl chloromethyl ether (Aldrich) with anhydrous HBr in dichloromethane at 0°C gave highest selectivity.

9 a) Interestingly, whereas hydrolysis of the enol ether **9** with 4:1 ether/35% perchloric acid initially (1 h) afforded a mixture of two epimers, prolonged treatment under the same conditions (overnight stirring, 12 h) yielded predominantly the slow moving isomer **10a**. TLC: (9:1 hexane/ethylacetate) $R_f = 0.24$ for **10a** and 0.28 for epimer **10b**.
b) The α-proton of the major aldehyde **10a** was shifted upfield and appeared as a broad multiplet with two large diaxial couplings (2.3 ppm, J = 10.7, 11.3, 3.6 ppm) compared to that of the minor epimer **10b** (2.65 ppm, narrow multiplet) suggesting the axial and equatorial positions of the α-protons of **10a** and **10b** respectively. Additionally, the aldehyde proton of the major epimer **10a** was shifted upfield compared to that of the minor epimer **10b** (9.58 ppm vs. 9.77 ppm), which conforms the trend of equatorial aldehyde proton appearing upfield relative to the axial aldehyde.

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11 a) In compound **12**, stereochemistry around the cyclohexyl ring is relative and not absolute, since it is actually an inseparable mixture of two diastereomers obtained by reaction of racemic aldehyde **10a** with the homochiral β-ketophosphonate **11**. Thus, the final target molecules **2a** and **2b** are mixtures of two diastereomers.
b) The relative all equatorial stereochemistry of the the substituents around the cyclohexyl ring system was once again confirmed by the fact that the allylic H_c proton of the major isomer **12** appeared as a broad multiplet, revealing axial-axial couplings, and was shifted upfield (2.2 vs. 2.7 ppm) compared to the narrow multiplet of the allylic proton of the minor epimer of **12**.
c) The epimeric impurity (approx. 5%) was readily removed in the next step upon desilylation of **12**.

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