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A NEW STRATEGY FOR THE SYNTHESIS OF MEVINIC ACID ANALOGUES

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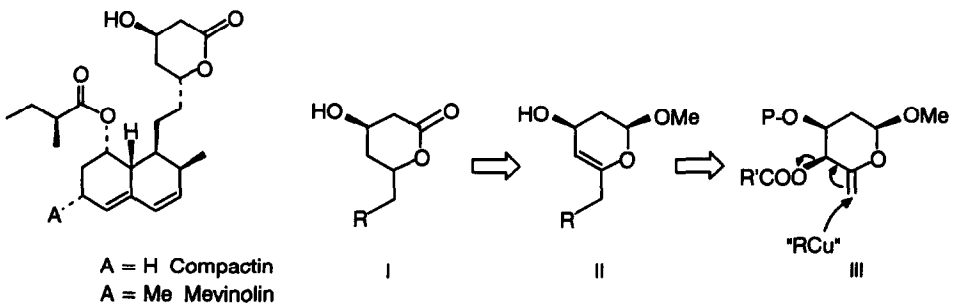
Abstract: The reaction of the allylic carbonate 2 with organocopper derivatives is the key step of a new strategy for the synthesis of mevinic acid analogues.

Since their discovery, mevinic acids compactin[1] and mevinolin[2] have attracted considerable interest because of their biological properties as inhibitors of 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGR), the rate-limiting enzyme of human cholesterol biosynthesis. The potential use of mevinic acids as therapeutic agents against atherosclerosis has prompted numerous synthetic works aimed at the preparation of mevinolin and compactin[3] and a lot of even more bioactive analogs.[4] From these studies, it appears that two crucial synthetic problems are to be solved to devise a competitive synthesis. One needs first a concise preparation of a suitably protected chiron[5] of the lactonic moiety in a limited number of steps.[3,6] Furthermore, the formation of the carbon-carbon bond between both parts of the molecule is not obvious, since side reactions such as 5,6 elimination or epimerisation of the lactonic precursor have been reported.[7]

We described several years ago, for the first time, the efficient SN2' displacement of carbohydrate allylic esters with organocopper derivatives occuring at the γ position of the allylic system with net inversion.[8,9] This method allowed the stereospecific introduction of a carbon chain at C-2 of a hexopyranose.[10] We took advantage of such an allylic substitution to devise a new strategy for the synthesis of mevinic acids analogs I that combines deoxygenation at C-4 and chain extension at C-6 of a carbohydrate.

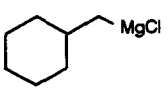
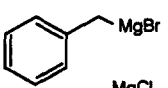
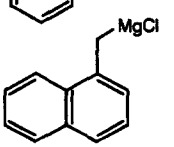
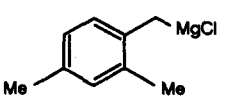
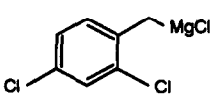


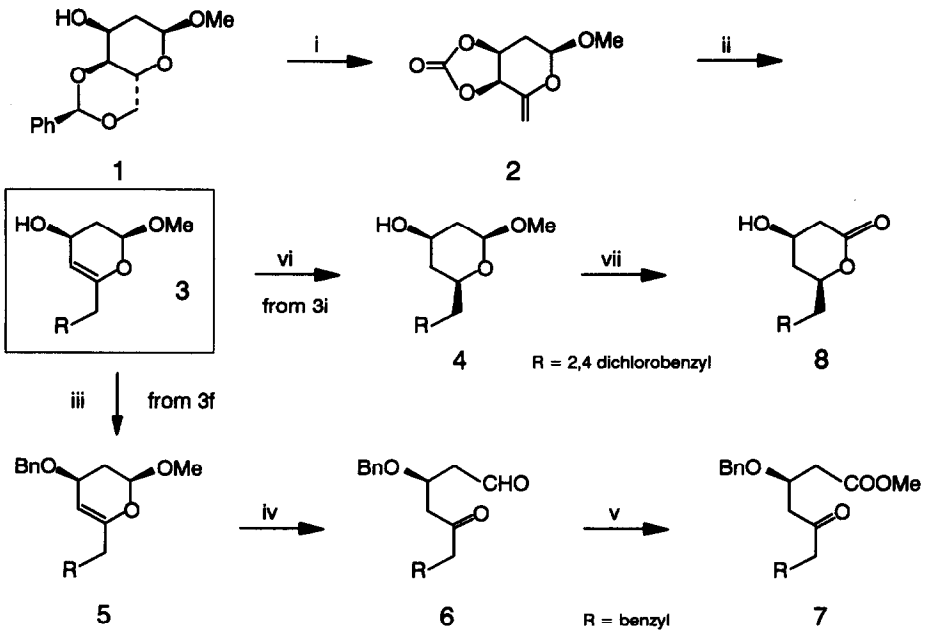
Scheme 1

According to the retrosynthetic analysis depicted in Scheme 1, the allylic carbonate **2** was chosen as the key intermediate and prepared in 4 steps from the known alcohol **1**.[11] The carbonate function had the unique advantage to activate the C-4 position and to be an immolative protecting group of the C-3 position, thus avoiding subsequent deprotection. The reactivity of the compound **2** with different organocopper species was first evaluated. Some cuprates derived from readily available alkyllithiums and different copper salts were examined. As seen from the table (entries 1-4), fair to excellent yields were obtained, especially using the combination of equimolecular amounts of alkyllithium and copper cyanide.[12] The problem of introducing more complex structures onto **2** was next confidently addressed. In this regard, the use of more readily available Grignard derivatives instead of lithio compounds would be of interest. In the light of the above results and literature precedents,[13] copper cyanide was used in combination with several alkyl magnesium derivatives (entries 5-9). By this way, a serie of olefins **3** was obtained in good yields.

The transformation of enol ethers **3** into 5-keto derivatives would be of interest, because it is known from the work of Heathcock[14] that 5-keto analogues of mevinic acids are often inhibitors of HMGR, as potent as the parent 5-hydroxy compounds. As an exemple the olefin **3f** has been transformed into the keto-ester **7**, the corresponding free hydroxy acid has been reported to be a good inhibitor of HMGR.[15] Thus, benzylation of the hydroxyl function of **3f** gave **5** in 80% yield, which upon acid hydrolysis gave the keto-aldehyde **6**, readily oxidized[16] into the keto-ester **7** in 55% overall yield.

Table. Reaction of the carbonate 2 with organocopper derivatives

Entry	"RCu from RLi or RMgX[17]	Product	Time (mn)	Yield (%)
1	MeLi	**3a**	35	59
2	BuLi	**3b**	30	95
3	tBuLi	**3c**	60	66
4	PhLi	**3d**	35	89
5		**3e**	20	60
6		**3f**	35	70
7		**3g**	30	50
8		**3h**	20	55
9		**3i**	40	65



Scheme 2. Reagents: (i) a) NBS, CCl_4,90%; b) MeONa, MeOH, quant.; c) carbonyldiimidazole, THF, 70%; d) DBU, THF, 82%; (ii) see ref. 17; (iii) NaH, BnBr, DMF, 80%; (iv) HCl 1N, THF, 85%; (v) Br_2, MeOH, $NaHCO_3$, 65%; (vi) H_2, Rh/Al_2O_3 5%, EtOH, 72%; (vii) a) HCl 1N, THF; b) NIS, Bu_4NI, CH_2Cl_2, 80% overall.

Further elaboration of compounds **3** to mevinic acid analogues required the reduction of the olefinic double bond and subsequent transformation into the needed lactone moiety. Thus, catalytic hydrogenation of **3i** was examined. Rhodium on alumina in ethanol[18] was used to prepare compound **4**. A single isomer was formed, as expected, the reduction occuring from the less hindered β side of olefin **3i**. The ^1H nmr spectrum of **4** was in agreement with the (*R*) stereochemistry at C-5 ($J_{1,2a} = J_{4a,5} = 10$ Hz) and the $^1C_4$ conformation. Acid hydrolysis of the acetal of **4**, followed by selective oxidation of the lactol[19] lead to the expected lactone **8**.[20] It is to note that the 5-(*R*) stereochemistry of compound **8** has to be inverted in order to have the 5-(*S*) configuration of the natural mevinic acids. This 5-(*S*) configuration could be reached either by diastereoselective reduction of the 5-keto derivatives or by inversion of the configuration at C-5 of the 5-(R) lactone[21] respectively. On the other hand the comparison of the biological activities of the 5-keto, 5-(*R*) and 5-(*S*) derivatives may provide with some more information about the active site of HMGR.[22]

The scope of this approach to mevinic acids analogues based on the reaction of sugar allylic carbonates with organocopper reagents, and the synthesis of some potential inhibitors of HMGR are now under current investigation.

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References

1) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.
Brown, A.G.; Smale, T.C.; King, T.J.; Hasenkamp, R.; Thompson, R.H. *J. Chem. Soc. Perkin Trans. I*, **1976**, 1165.

2) 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. U.S.A*, **1980**, *77*, 3957.

3) For a review see: Rosen, T.; Heathcock, C.H. *Tetrahedron*, **1986**, *42*, 4909.

4) Stokker, G.E.; Alberts, A.W.; Anderson, P.S.; Cragoe, E.J. Jr.; Deana, A.A.; Gilfillan, J.L.; Hirshfield, J.; Holtz, W.J.; Hoffman, W.F.; Huff, J.W.; Lee, T.J.; Novello, F.C.; Prugh, J.D.; Rooney, C.S.; Smith, R.L.; Willard, A.K. *J. Med. Chem.* **1986**, *29*, 170, and previous papers of this serie

5) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983.

6) For recent approaches from carbohydrates see Roth, B.D.; Roark, W.H. *Tetrahedron. Lett.* **1988**, *29*, 1255. David, C.; Gesson, J.P.; Jacquesy, J.C. *Tetrahedron. Lett.* **1989**, *30*, 6015.

7) Rosen, T.; Taschner, M.J.; Heathcock, C.H. *J. Org. Chem.* **1984**, *49*, 3994. Prugh, J.D.; Rooney, C.S.; Deana, A.A.; Ramjit, H.G. *J. Org. Chem.* **1986**, *51*, 648.

8) Chapleur, Y.; Grapsas, Y. *Carbohydr. Res.* **1985**, *141*, 153.

9) For a leading reference about the alkylation of allylic derivatives see: Underiner, T.L.; Paisley, S.D.; Schmitter, J.; Lesheski, L.; Goering, H.L. *J. Org. Chem.* **1989**, *54*, 2369.

10) Danishefsky et al. successfully applied this reaction in the total synthesis of avermectin: Danishefsky, S.J.; Armistead, D.M.; Wincott, F.E.; Selnick, H.G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967.

11) Prins, D.A. *J. Am. Chem. Soc.* **1948**, *70*, 3955. Richardson A.C., *Carbohydr. Res.*, **1967**, *4*, 422.

12) Levisalles, J.; Rudler-Chauvin, M.; Rudler, H. *J. Organomet. Chem.* **1977**, *136*, 103. For a review see: Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron*, **1984**, *40*, 5005.

13) For a review see: Erdik, E. *Tetrahedron*, **1984**, *40*, 641.

14) Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.*, **1987**, *30*, 1858.

15) Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197.

16) Williams, D.R.; Klinger, F.D.; Allen, E.E.; Lichtenthaler, F.W. *Tetrahedron Lett.*, **1988**, *29*, 5087.

17) For entries 1 to 4, three equivalents of the appropriate commercial alkyllithium were slowly added to a suspension of three equivalents of copper cyanide in diethylether at 0°C (8ml/mmol). After 20 min. at this temperature the solution was transferred onto a solution of the carbonate **2** in diethylether (10ml/mmol). For entries 5 to 9, the Grignard reagent prepared from the corresponding halide was added to a suspension of copper cyanide (10%mol) in tetrahydrofuran at O°C (8ml/mmol), and the resulting mixture was slowly added to the carbonate **2** (10ml/mmol).

18) Adams, J.; Frenette, R. *Tetrahedron Lett.* **1987**, *28*, 4773.

19) Hanessian, S.; Wong, D.H.; Thérien, M. *Synthesis* **1981**, 394.

20) For the synthesis and biological assay of (5-epi)-**8**, see Stokker, G.E.; Hoffman, W.F.; Alberts, A.W.; Cragoe, E.J. Jr.; Deana, A.A.; Gilfillan, J.L.; Huff, J.W.; Novello, F.C.; Prugh, J.D.; Smith, R.L.; Willard, A.K. *J. Med. Chem.* **1985**, *28*, 347.

21) For a lactonization with inversion of the alcohol configuration using the Mitsunobu reaction see: Valverde, S.; Garcia-Ochoa, S.; Martin-Lomas, M. *J. Chem. Soc. Chem. Commun.*, **1987**, 1714. Mitsunobu, O. *Synthesis*, **1981**, 1.

22) For discussions on the active site of HMGR see : Nakamura, C. E.; Abeles, R.H. *Biochemistry*, **1985**, *24*, 1364, and ref. 15

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