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Stereoselective Synthesis of the Tetrasubstituted Cyclohexane Core of a Monocyclic Mevinic Acid Analogue

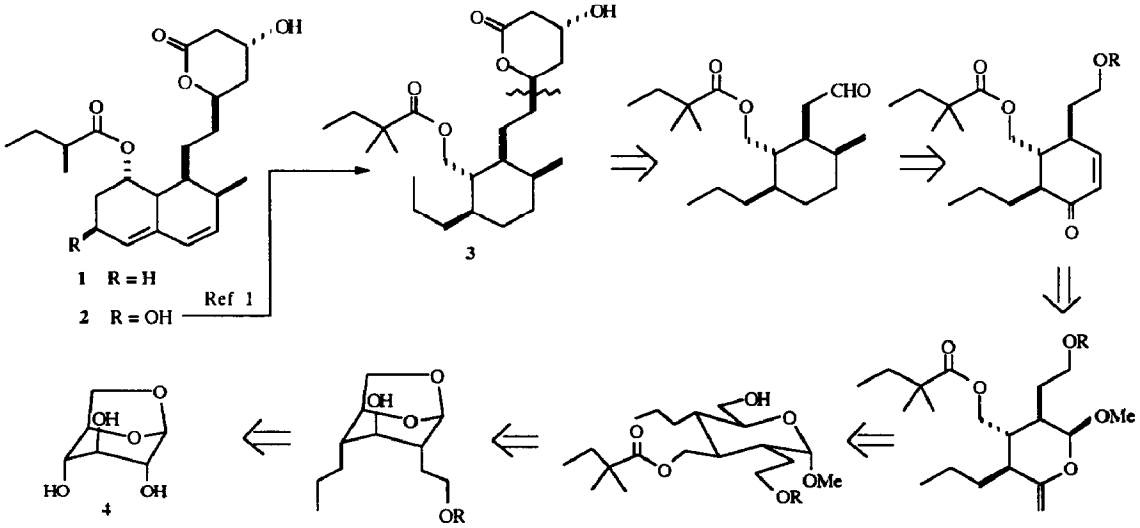
Mikhail S. Ermolenko*, Alain Olesker and Gabor Lukacs

Institut de Chimie des Substances Naturelles du C.N.R.S., 91198 Gif sur Yvette, France

Abstract: *Stereoselective synthesis of a 1,2,3,4-tetrasubstituted cyclohexane* **23**, *intermediate towards Karanewsky's monocyclic Compactin analogue* **3**, *has been performed starting from levoglucosan* **4**.

Structure-activity relationship studies of the mevinic acid family of HMG-CoA reductase inhibitors (e.g. Compactin **1**, Pravastatin **2**), potential agents for lowering plasma cholesterol[1], have also been extended to simplified monocyclic analogues[2]. These investigations led Karanewsky to synthesize the cyclohexane analogue **3**, from naturally occurring Pravastatin **2**, which exhibits improved inhibitory properties by an order of magnitude with respect to its decalin based counterpart[3]. These biological results prompted us to initiate a programme aimed at the total synthesis of **3**.

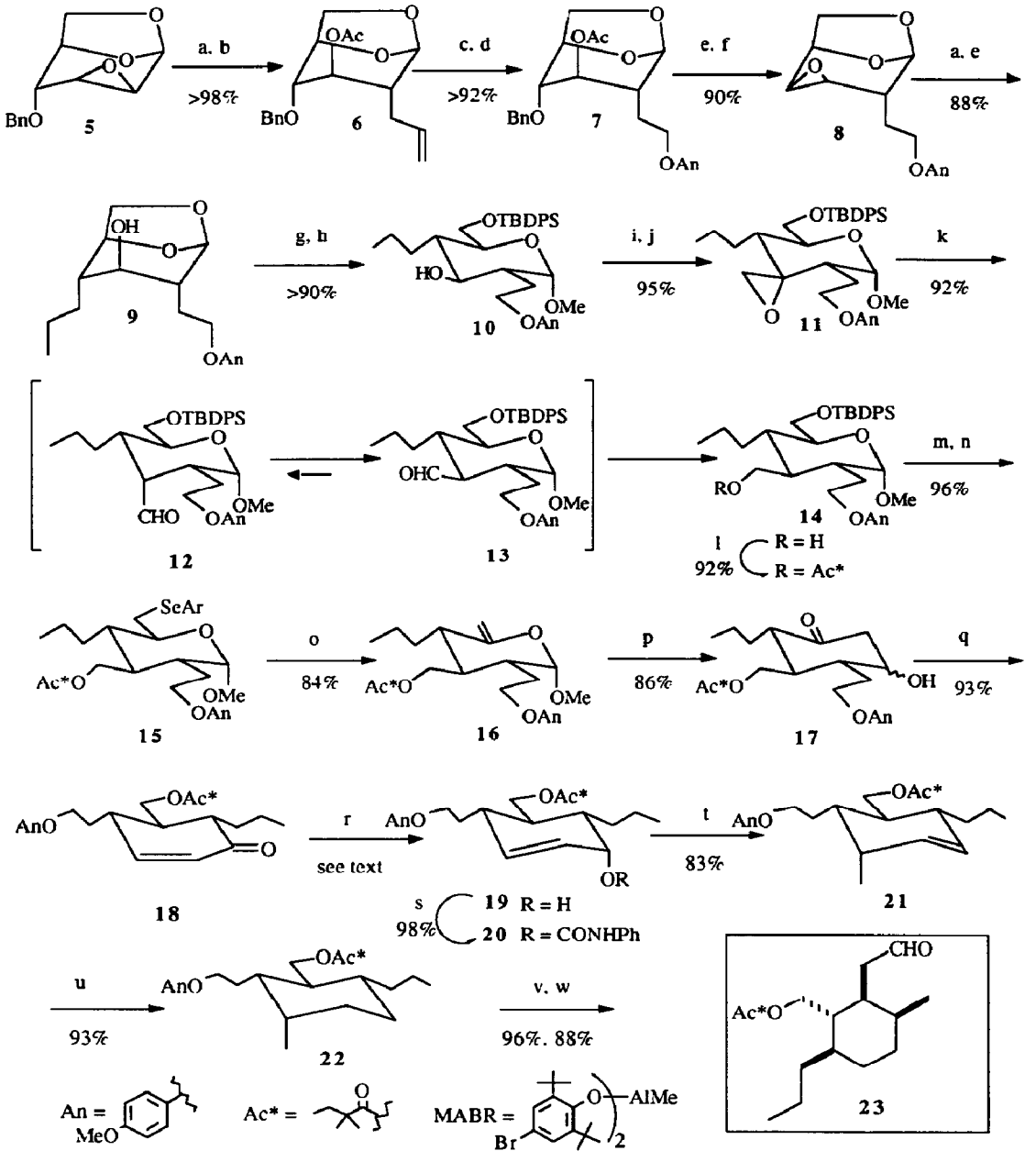
Intensive studies for more than a decade in this field have almost exhausted the synthetic approaches to the lactone portion of these molecules[1]. In contrast, the 1,2,3,4 - tetrasubstituted cyclohexane unit of **3** leaves more space for inspiration. One of such hitherto unexplored possibility is shown at the retrosynthetic scheme below.



Scheme 1

Oxirane ring opening of the known epoxide **5**[4] with All_2Mg proceeds regio- and stereospecifically in virtually quantitative yield[5]. After chain shortening of the allyl group of **6**, the resulting primary alcohol was protected as a p-methoxyphenyl ether[6] to give **7** which was converted to epoxide **8**. The propyl side chain of **9** was introduced by treatment of **8** with All_2Mg followed by hydrogenation. The bicyclic acetal **9** was then subjected to acidic methanolysis and the methyl glycosides (ca. 85 : 15) were separated. The minor β-anomer was re-equilibrated in the same condition thus providing additional portion of the α-methyl glycoside which was selectively protected by silylation at its primary hydroxyl to give **10**. Oxidation of the secondary hydroxyl group of **10** gave the ketone which was transformed into the diastereomerically pure spiroepoxide **11** by Matteson's method[7]. Upon treatment with 2 equiv. of methylaluminium bis-(4-bromo-2,6-di-tert-butyl-phenoxide) (MABR[8]) spiroepoxide **11** underwent a clean stereoselective isomerisation to the axial aldehyde **12** which can be obtained in pure form after chromatographic separation from residual phenol. Brief exposure of **12** to saturated methanolic potassium carbonate gives an unseparable mixture of **12** and its isomer **13** (**12** : **13** = 23 : 77 at the equilibrium). Reduction of this mixture, separation of the resulting primary alcohols and recycling of the minor axial isomer by oxidation-reduction, affords **14** in good overall yield. However, it was found that, at low temperature, the equatorial aldehyde **13** is reduced much faster than **12**. Isomerisation of **12** was followed by reduction with 0.6 equiv. $NaBH_4$ at -20°C for 15 minutes, this treatment was repeated and furnished the required equatorial hydroxymethyl derivative **14** in excellent yield. The primary hydroxyl group of **14** was acylated[9] with 2,2-dimethylbutyric acid and after desilylation and elimination via the selenoxide method[10], Δ^5-enopyranoside **16**, a substrate for the Ferrier rearrangement, was obtained. The absence of electronegative substituents on the pyranoside ring made **16** extremely labile. Thus, in an attempted catalytic Ferrier reaction[11], *addition of 10 mol.% of $Hg(OCOCF_3)_2$ to an aqueous acetone solution of* **16** resulted in a very rapid and complete consumption of the substrate, the main reaction product being an acyclic keto-aldehyde as a result of a simple hydrolysis. However, *slow addition (1 hour) of* **16** *in the same solvent mixture to 10 mol.% $Hg(OCOCF_3)_2$* gave rise, in good yield, to the desired β-hydroxycyclohexanone **17** as a 2 : 1 mixture of isomers at the carbinol centre. Elimination via the derived mesylate gave cyclohexenone **18**.

With the latter compound in hand, the only remaining problem was the introduction of a methyl group in α-cis position relative to the hydroxyethyl side chain. Various unsuccessful attemps brought us to the conclusion that the only practical way to the desired product **21** would be a syn-S_N2' type substitution in carbamate **20**[12], prepared from the corresponding allylic alcohol **19**. Numerous attemps to selectively reduce **18** failed: a mixture of **19** and the corresponding equatorial alcohol was invariably obtained, sometimes contaminated by saturated products. The acetate of the equatorial alcohol afforded, on treatment with $Me_5Cu_3Li_2$[12], a mixture of **21** and its regiomer without double bond displacement (1 : 2), and was thus useless for the synthesis. The best solution we found was the regioselective reduction of enone **18** with the $NaBH_4$-$CeCl_3$·7 H_2O system[13], separation of the mixture of epimeric alcohols, and recycling of the unwanted equatorial alcohol[14]. Substitution of the carbamate group in **20** with $Me_5Cu_3Li_2$ proceeded with complete regio- and stereocontrol to give **21** in good yield. Although the remaining part of the synthesis appeared straightforward, hydrogenation of the isolated double bond in **21** over Pd/C resulted in a mixture of four products suggesting intermediate π-allylic species. Fortunately, hydrogenation of **21** over hydrogen-presaturated Rh/Al_2O_3 in toluene solution at 0°C led almost exclusively to the long-awaited product **22**. The p-methoxyphenyl protecting group was oxidatively cleaved and the primary alcohol was oxidized to give the oxygen-sensitive aldehyde **23**[15] which was immediately used in the coupling reaction with the lactone portion precursor, as described in the next paper.



a. All2Mg/Et2O, rt; b. Ac2O-Et3N, DMAP (cat)/CH2Cl2, rt; c. NMO-OsO4 (cat)/t-BuOH, then H5IO6, then NaBH4/EtOH, rt; d. p-MeOC6H4OH, DEAD-Ph3P/CH2Cl2, rt; e. H2, Pd/C/MeOH; f. MsCl-Et3N/CH2Cl2, -10°, then MeONa/MeOH, rt; g. MeOH-H+ (separn, equlbrn); h. TBDPSCl/Py; i. Swern oxdn; j. ICH2Cl-MeLi/THF, -78°; k. MABR/CH2Cl2, -78°, then K2CO3/MeOH, then NaBH4; l. Ac*OH-MsCl, Et3N, DMAP/CH2Cl2; m. Bu4NF/THF; n. o-NO2C6H4SeCN-Bu3P/THF; o. NaIO4/MeOH, then PhMe-Et3N, Δ; p. Hg(OTFA)2 (cat)/(CH3)2CO-H2O (4 : 1); q. MsCl-Et3N/CH2Cl2, -10° to rt; r. >2eq. CeCl3·7H2O, NaBH4/MeOH; s. PhNCO, DMAP/Py; t. Me5Cu3Li2/Et2O; u. H2, Rh/Al2O3, PhMe; v. CAN/MeCN-H2O; w. PCC, MS 4Å/CH2Cl2.

Scheme 2

References and Notes

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4. Available from levoglucosan in 4 steps in 50-55% overall yield according to Grindley, T. B.; Reimer, G. J.; Kralovec, J.; Brown, R. G.; Anderson, M. *Can. J. Chem.* **1987**, *65*, 1065-1071.

5. Diallylmagnesium was prepared by precipitation of the $MgCl_2 \cdot$1,4-dioxane complex from AllMgCl/ether; the resulting suspension was used as such (cf. Kochetkov, N. K.; Sviridov, A. S.; Ermolenko, M.S. *Tetrahedron Lett.* **1981**, *22*, 4315-4318).

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10. Selenoether **15** was prepared by slow (1 hr) addition of ArSeCN in THF to a mixture of the substrate and Bu_3P in the same solvent at r.t.; fast addition, or addition of Bu_3P to a mixture of substrate and ArSeCN according to the procedure described by Grieco (Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486) gave **15** in 60-65% yield only.

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14 At least 2 equiv. of $CeCl_3 \cdot 7H_2O$ (one equiv. for each carbonyl group present in **18**) are to be used to prevent conjugate reduction of enone; the ca. 1 : 1 mixture of stereoisomeric allylic alcohols obtained quantitatively was separated and the unwanted equatorial isomer recycled by Swern oxidation in >96% yield.

15. All new compounds gave spectral and analytical data consistent with the assigned structure. Specific rotations were measured in $CHCl_3$ solution, using c = 1.0. Selected data: **6** : +10°; **7** : -18°; **9** : -43°; **10** : +45°; **11** : +58°; **14** : (R = H) +45° and (R = Ac*) +35°; **15** : +22°; **18** : +41°; **19** : -23°; **20** : -105°; **21** : -5°; **22** : -7°; **23** : -9°.

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