Tetrahedron Letters, Vol. 33, No. 29, pp. 4183-4186, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

New Chiral Blocks for Introducing the Side Chain of HMG-CoA Reductase Inhibitors

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Summary: A couple of versatile building blocks (8 and 9) of the side chain portion found in many HMG-CoA reductase inhibitors have been prepared. The successful introduction of the side chain to an aromatic ring by 8 or 9 has been demonstrated.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes a critical step in the biosynthesis of cholesterol. Compactin and mevinolin[1] reported in 1976 and 1980 respectively are natural products to show potent inhibitory effects against HMG-CoA reductase and thus find use as hypocholesterolemic agents. Since then, a great number of artificial HMG-CoA reductase inhibitors related to these compounds have been developed and are still under active investigation. Fig. 1 illustrates such inhibitors **1**[2,3,4] (or their acid form **2**) which are characterized by optically active 3-hydroxy valerolactone and an aromatic ring (Ar, which is sometimes replaced with an alkenyl group) combined by *trans*-ethylene bridge.

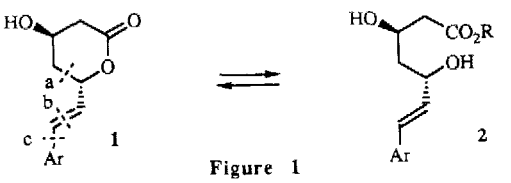
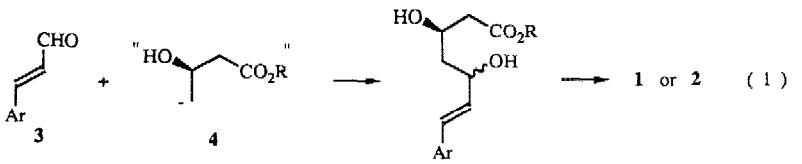
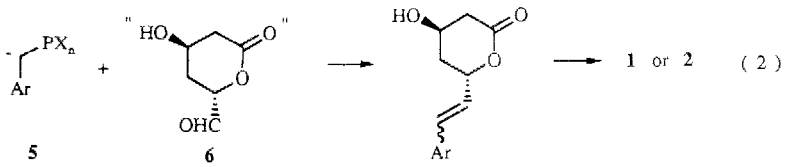


Figure 1

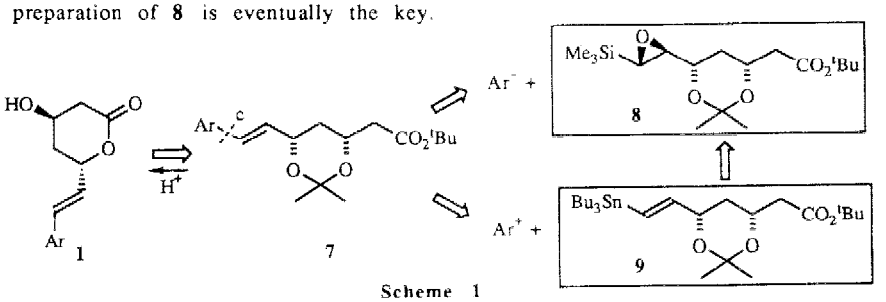
In order to screen the variable aromatic moieties, a method allowing a quick assembly of the *trans*-olefin having the essential hydroxy lactone and the aromatic rings would be very helpful. However, this process mostly accompanies a cleavage of the lactone (scission a in Fig. 1)[2] or that of the olefin (scission b),[3] requiring, for example, the aldehyde **3** and the synthetic equivalent of **4** (eq 1), or the Wittig reagent **5** and the synthetic equivalent of **6** (eq 2) as precursors. The ambiguity associated with a control of the absolute stereochemistry at the 5-position of the lactone or a *cis/trans* purity of the resulting olefin has required tedious optimizations of reaction conditions and/or separations of isomers from substrate to substrate.





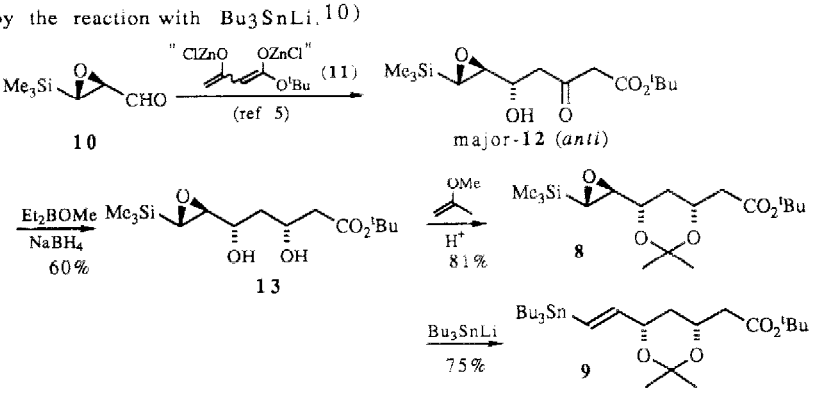
5 6 (2)

We conceived that the scission c (Fig. 1)[4] would be more straightforward in rapid screening of the aromatic moieties provided that a precursor allowing the introduction of the *trans*-ethylene group as well as the optically active hydroxy lactone is available. To make the applicability of this methodology as general as possible, we chose **8** and **9** for such candidates as shown in Scheme 1: the former reacts with *anionic* species of aromatics to give the desired product **7** while the latter does with *cationic* species. Since **9** would be derived from **8**, the preparation of **8** is eventually the key.



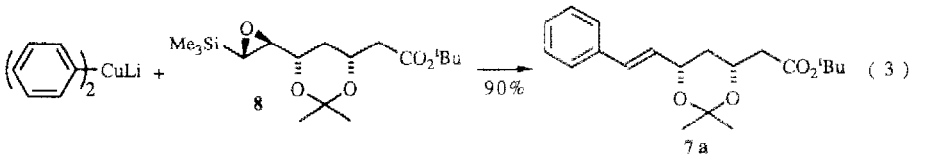
Scheme 1

To attest the feasibility of this process, we focused our attention on a concise preparation of **8** which is shown in Scheme 2. Treatment of the optically active epoxy aldehyde **10** (>98% ee) with organozinc compound of the acetoacetate **11** as described in the accompanied paper[5] gave a mixture of the two diastereoisomers of **12** which were separated by flash chromatography on silica gel.[6,7] The *syn*-reduction of major-**12** (>96% de, *anti* configuration (*vide infra*)) was carried out by an improved method ($Et_2BOMe/NaBH_4$)[8] to afford the desired *syn*-diol **13** in good yield, yet somewhat lower than those of usual 1,3-diols due to the formation of a by-product (**14**[9]) resulting from a concomitant epoxide opening of **13** under these reaction conditions. Protection of the diol with acetonide in a standard manner furnished the key compound **8** which was, in turn, led to another essential precursor **9** by the reaction with Bu_3SnLi.[10]



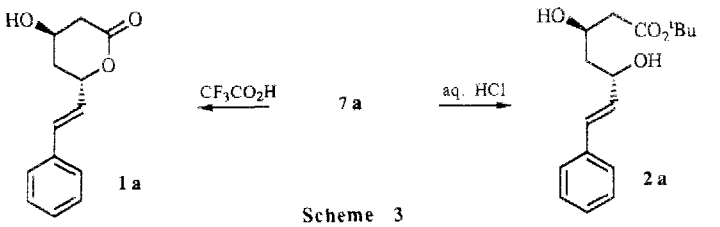
Scheme 2

Having succeeded in the preparation of both **8** and **9**, we were at the final stage to introduce the side chain to an aromatic ring. Ph_2CuLi was treated with the chiral unit **8** to give the desired coupling product **7a** with the olefin being exclusively *trans* in excellent yield (eq 3),[11,12] demonstrating that **8** works quite well to introduce the side chain to the Ar^- species in Scheme 1. Alternatively, PhBr reacted with the vinyltin **9** in the presence of a palladium catalyst to afford **7a** again in good yield (eq 4).[13] Thus incorporation of the side chain to cationic species of aromatics (Ar^+ in Scheme 1)[14] has been realized with **9**.



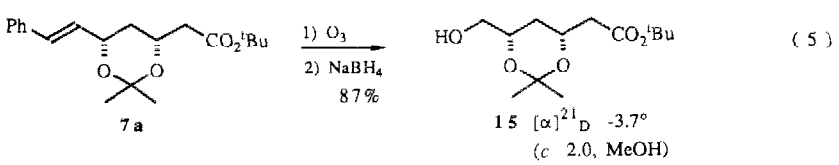
It is noteworthy that complementary use of **8** and **9** makes this methodology suitable for a wide variety of substrates without worry about isomeric purities of products.

The lactone **1a** can be prepared from **7a** by a treatment with CF_3CO_2H[3b] or alternatively, deprotection of the acetonide moiety of **7a** with hydrochloric acid (to **2a** in 96% yield) followed by saponification and lactonization[2b,f] also gives **1a** (Scheme 3).



Scheme 3

The structural confirmation of the resulting side chain was made by the following sequence (eq 5): ozonolysis of **7a** (prepared by the Ph_2CuLi method) in methanol followed by the immediate reduction with $NaBH_4$ afforded the alcohol **15** whose ^1H nmr spectrum and $[\alpha]_D$ value are in good agreement with those of an authentic sample.[3b] Thus the absolute configuration as well as the relative one and a high optical purity of **7a** have been verified, which unambiguously determined that the major isomer of **12** has the *anti*-configuration.[5]

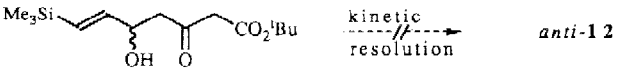


In summary, chiral units **8** and **9** useful for introduction of the side chain of HMG-CoA reductase inhibitors have been developed. Synthesis of some medicinally active inhibitors having an appropriate aromatic ring based on this methodology is our current interest.

Acknowledgement: The authors are grateful to Dr. G. Wess of Hoechst AG, Germany for informing us the $[\alpha]_D$ value of the authentic sample of **15**.

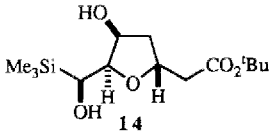
References and Notes

1) Review: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.
2) Recent reports for the scission a: (a) Roth, B. D.; Bocan, T. M. A.; Blankley, C. J.; Chucholowski, A. W.; Creger, P. L.; Creswell, M. W.; Ferguson, E.; Newton, R. S.; O'Brien, P.; Picard, J. A.; Roark, W. H.; Sekerke, C. S.; Sliskovic, D. R.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 463; (b) Sit, S. Y.; Parker, R. A.; Motoc, I.; Han, W.; Balasubramanian, N.; Catt, J. D.; Brown, P. J.; Harte, W. E.; Thompson, M. D.; Wright, J. J. *J. Med. Chem.* **1990**, *33*, 2982; (c) Prugh, J. D.; Alberts, A. W.; Deana, A. A.; Gilfillian, J. L.; Huff, J. W.; Smith, R. L.; Wiggins, J. M. *J. Med. Chem.* **1990**, *33*, 758; (d) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; v. Kerekjarto, B.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61; (e) Johnson, W. S.; Kelson, A. B.; Elliott, J. D. *Tetrahedron Lett.* **1988**, *29*, 3757; (f) Reddy, G. B.; Lynch, J. E.; Volante R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385.
3) Recent reports for the scission b: (a) Escudier, J.-M.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1991**, *32*, 5345; (b) Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, *31*, 2545; (c) Prasad, K.; Chen, K.-M.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 307; (d) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A,; Jendralla, H.; Kesseler, K.; Wess, G.; Schubert, W.; Granzer, E.; Kerekjarto, B. v.; Krause, R. *Tetrahedron Lett.* **1988**, *29*, 929.
4) This process is quite rare. A recent example for the scission c: Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 31, which relied on the Heck reaction and met with limited success.
5) Urabe, H.; Matsuka,T.; Sato, F. the preceding paper.
6) In a multi-gram scale one chromatography afforded a sample of the major-**12** of 96% de in about 40% yield together with inseparable portions of both isomers which may be recycled.
7) Unfortunately, a kinetic resolution of **16** by the Sharpless asymmetric epoxidation was found to be useless in this case. See note 11 in ref 5.



16

8) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923.
9) The by-product **14** is most likely to have the following structure based on its ^1H nmr spectrum and a mechanistic consideration.



14

10) Kobayashi, Y.; Shimazaki, T; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 5849.
11) Hudrlik, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2264.
12) The above transformations proceeded equally well starting from the minor(*syn*)-**12** (**N'** refers to another diastereoisomer or enantiomer of **N**): minor-**12**→**13'**, 75%; **13'**→**8'**, 80%; **8'**→**7a'**, 85%. A ^1H nmr spectrum of the final product **7a'** was identical with that of **7a** prepared from major-**12**. Thus **8'**, a diastereoisomer of **8**, may be useful for the preparation of the inhibitors with the unnatural configurations at the 3- and 5-positions of lactone.
13) Corriu, R. J. P.; Bolin, G.; Moreau, J. J. E. *Tetrahedron Lett.* **1991**, *32*, 4121.
14) ArBr would be substituted with ArOTf and the palladium-catalyzed coupling reactions of highly hindered aryl and alkenyl triflates with vinyltin compounds have been reported: Saa, J. M.; Martorell, G.; Garcia-Raso, A. *J. Org. Chem.* **1992**, *57*, 678; Scott, N. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

(Received in Japan 23 March 1992)