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Enantioselective allyltitanation. Application to the synthesis of lactone units related to compactin and mevinolin

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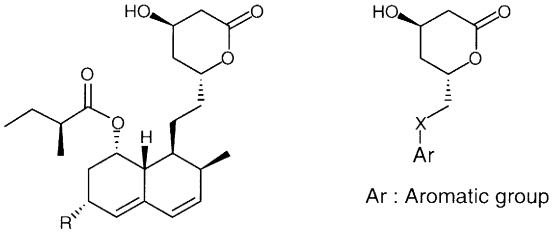
Abstract

The enantioselective convergent synthesis of two different models of the lactone units of compactin and mevinolin was achieved using two consecutive enantioselective allyltitanations of aldehydes. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: allyltitanation; 1,3-diols; lactones; compactin; mevinolin.

Compactin and mevinolin are fungal metabolites that are potent inhibitors of cholesterol biosynthesis at the level of the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG–CoA reductase).[1] The important implications for the treatment of coronary artery disease have made these compounds the subject of intense research aimed at biological evaluation, chemical synthesis and modification of the natural products. A plethora of work has been directed toward the preparation of synthetic analogues of types **A** and **B**.[2] In compounds of type **A** (X=CH_2), and **B** (X=O) the stereochemically complex hexahydronaphthalene moiety of compactin and mevinolin has been replaced by suitably substituted achiral aromatic moieties and open-chain moieties. Compounds of type **A**, that exceed the in vitro and in vivo activity of mevinolin, have been described.[3]



Compactin R = H
Mevinolin R = CH_3

A: X = CH_2
B: X = O

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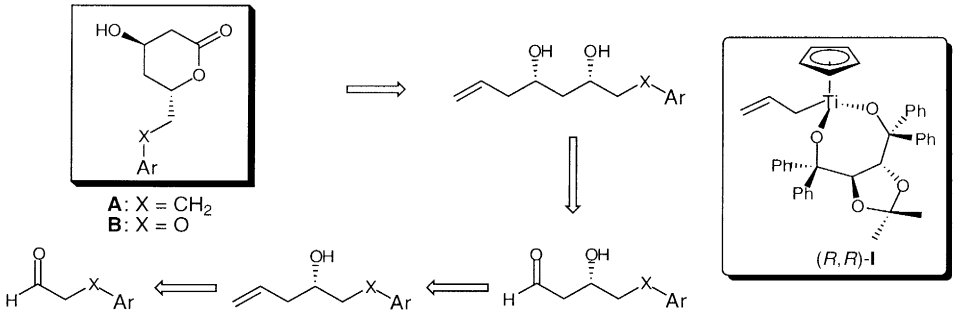
Although, in recent years, these compounds have been the targets of an increasing number of synthetic efforts, their synthesis remains a challenge. Introduction of the required stereocenters at position C-3 and C-5 of the lactone is vital for the biological activity and has proved to be an important synthetic feature. Consequently, a number of enantioselective or specific syntheses of the lactone moiety have appeared involving the elaboration of chiral pool materials such as tartaric acid,[4] L-amino acids,[5] (*S*)-malic acid,[6] and carbohydrates.[7] Similary, asymmetric syntheses involving an asymmetric Diels–Alder reaction,[8] a diastereoselective aldol reaction,[9] an asymmetric epoxidation,[10] enantioselective reductions of prochiral β,δ-diketo esters[11] or 1,3-diketones,[12] diastereoselective reduction of an optically active β,δ-diketo sulfoxides esters,[13] and an enantioselective deprotonation reaction of prochiral compounds with chiral bases have also been reported.[14]

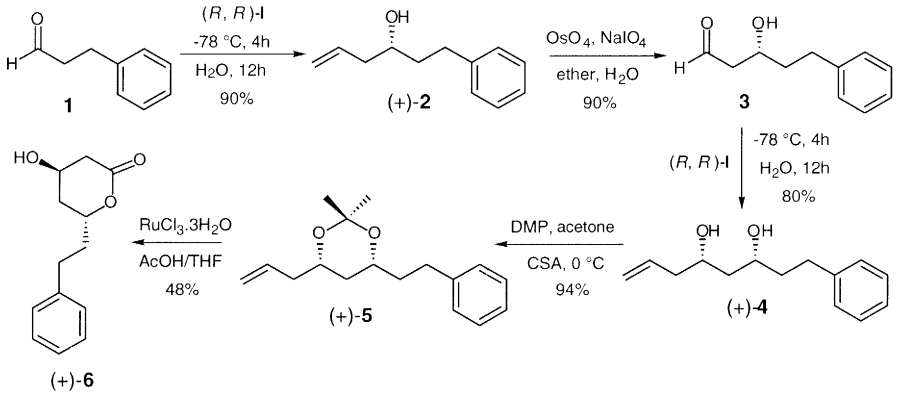
Here, we report the synthesis of lactones of type **A** and **B**, using two consecutive enantioselective allyltitanations of aldehydes which employ the cyclopentadienyldialkoxyallyltitanium complex (*R*,*R*)-**I**,[15] according to the following retrosynthetic Scheme 1.



Scheme 1. Retrosynthetic analysis

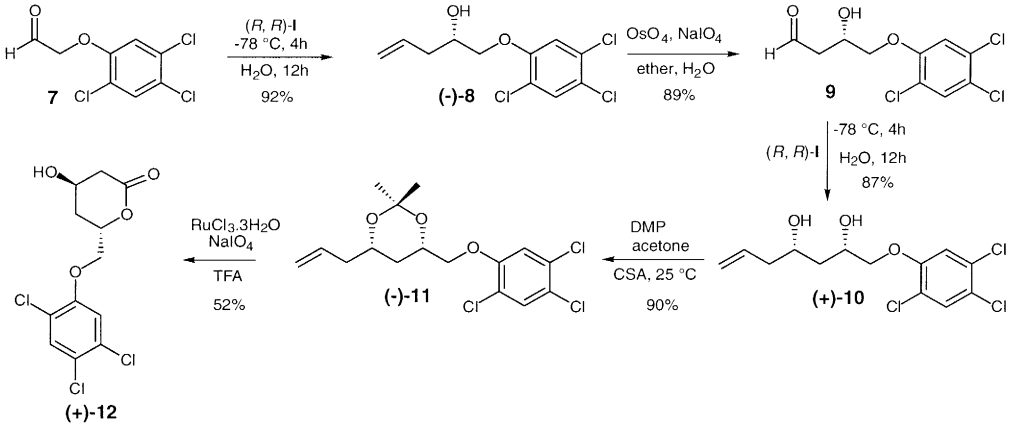
The lactone of type **A** (X=CH_2; Ar=Ph) was synthesized from the cheap, commercially available 2-phenylpropionaldehyde **1** by two consecutive enantioselective allyltitanations. Addition of the cyclopentadienyldialkoxyallyltitanium complex (*R*,*R*)-**I**,[15] to 2-phenylpropionaldehyde **1** led to the homoallylic alcohol (+)-**2** in good yield (90%)[16] and with excellent enantiomeric excess (93%) ($[\alpha]_D^{22}$=+19 (*c* 2.8, $CHCl_3$)).[17] This alcohol was then transformed to aldehyde **3** ($NaIO_4/OsO_4$ in H_2O/ether) which was directly treated with complex (*R*,*R*)-**I** at −78°C to furnish 1,3-diol (+)-**4** ($[\alpha]_D^{22}$=+16 (*c* 1.1, $CHCl_3$); yield=80%). The allyltitanation of **3** did not require the protection of the hydroxy group and the *syn* 1,3-diol (+)-**4** was obtained with a good diastereoselectivity (de=95%). The relative configuration of the 1,3-diol (+)-**4** was determined by converting it to the corresponding acetonide (+)-**5** (2,2-dimethoxypropane-acetone/CSA, $[\alpha]_D^{22}$=+20 (*c* 2.7, $CHCl_3$); yield=94%) and by analyzing its ^{13}C NMR.[18] After oxidation of (+)-**5** ($RuCl_3 \cdot 3H_2O/NaIO_4$) and aqueous acetic acid treatment ($AcOH/H_2O$/THF) the hydroxy lactone (+)-**6**, which represents the top portion of compactin and mevinolin, was obtained ($[\alpha]_D^{22}$=+50 (*c* 0.85, $CHCl_3$); yield=48%).[6,12] The hydroxy lactone (+)-**6** was synthesized in six steps from 2-phenylpropionaldehyde with an overall yield of 29% (Scheme 2).

The enantioselective allyltitanation also allowed the synthesis of lactones of type **B** (X=O). As an example of this type, the synthesis of lactone (+)-**12** has been realized from aldehyde **7** which was obtained from 2,4,5-trichlorophenol.[19] Aldehyde **7** was converted to the optically active homoallylic alcohol (−)-**8** in 92% yield ($[\alpha]_D^{22}$=−5 (*c* 2.8, $CHCl_3$); ee=95%) by using complex (*R*,*R*)-**I**.[17] After oxidation of (−)-**8** ($OsO_4/NaIO_4$, H_2O/ether), the aldehyde **9** was obtained and transformed to (+)-**10** ((*R*,*R*)-**I**, Et_2O, −78°C); de=95%; $[\alpha]_D^{22}$=+11 (*c* 2.4, $CHCl_3$); yield=87%). This compound was then converted to acetonide (−)-**11** (2,2-dimethoxypropane-acetone/CSA; $[\alpha]_D^{22}$=−12 (*c* 1.1, $CHCl_3$); yield=90%), which was oxidized ($RuCl_3 \cdot 3H_2O/NaIO_4$, $CH_3CN/CCl_4/H_2O$) and treated with aqueous TFA in CH_2Cl_2 at



Scheme 2. Synthesis of lactone of type **A** (X=CH_2)

25°C to afford the hydroxy lactone (+)-**12** ($[\alpha]_D^{22}$=+12 (*c* 0.78 $CHCl_3$); yield=52%).[20] The synthesis of lactone (+)-**12** was achieved with good yield and good diastereomeric excess by using two consecutive allyltitanations (Scheme 3).



Scheme 3. Synthesis of lactone of type **B** (X=O)

In summary, the enantioselective allyltitanation of aldehydes represents a new way for enantioselective generation of the (*R*,*R*)-lactone unit of compactin and mevinolin and it allows the elaboration of analogous lactone systems.

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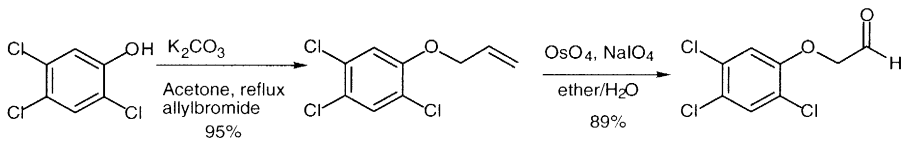
References

1. (a) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165–1170; (b) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346–1348; (c) Endo, A. *J. Antibiot.* **1979**, *32*, 852–854.

2. Jendralla, H.; Granzer, E.; von Kerekjarto, B.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L. J.; Granata, S.; Herchen, J.; Kleine, H.; Schussler, H.; Wagner, K. *J. Med. Chem.* **1991**, *34*, 2962–2983.
3. *Drugs of the Future* **1987**, *12*, 437–442.
4. Minami, T.; Takahashi, K.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 513–516.
5. (a) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Carganico, G. *J. Org. Chem.* **1990**, *55*, 5766–5777; (b) Menges, M.; Brückner, R. *Synlett* **1993**, 901–905.
6. Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101–2104.
7. (a) Miyazawa, K.; Yoshida, N. *Chem. Lett*. **1993**, 1529–1530; (b) Ermolenko, M. S.; Olesker, A.; Lukas, G. *Tetrahedron Lett.* **1994**, *35*, 711–714 and 715–718; (c) Roth, B. D.; Roark, W. H. *Tetrahedron Lett.* **1988**, *29*, 1255–1258.
8. Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935–938.
9. Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385–1388.
10. Bonadies, F.; Di Fabio, R.; Gubbiotti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.* **1987**, *28*, 703–706.
11. (a) Shao, L.; Seki, T.; Kawano, H.; Saburi, M. *Tetrahedron Lett.* **1991**, *32*, 7699–7702; (b) Bennett, F.; Knight, D. W.; Fenton, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 133–140; (c) Ansari, M. H.; Kusumoto, T.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 8271–8274.
12. Compound (+)-**6** is showing all the characteristics described in the literature: Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem*. **1991**, *56*, 5161–5169.
13. Solladié, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 7774–7777.
14. Honda, T.; Ono, S.; Mizutani, H.; Hallinan, K. O. *Tetrahedron: Asymmetry* **1997**, *8*, 181–184.
15. (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501–504.
16. This reaction was achieved on 0.2 g of **1** and on 0.5 g of **7**.
17. The enantiomeric excess of **8** and **12** was determined by HPLC analysis, Chiralcel-AD_2 column (hexane:isopropanol).
18. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.
19. Preparation of compound **7**:



20. Colorless solid. mp: 90–92°C; $[\alpha]_D^{22}$=+12 (*c* 0.78, $CHCl_3$); IR: 3405, 2935, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42 (s, 1H), 7.01 (s, 1H), 5.10 (m, 1H), 4.55 (m, 1H), 4.3–4.10 (m, 2H), 2.80–2.68 (m, 2H), 2.30 (br s, 1H, OH), 2.22–2.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2 (s), 152.8 (s), 131.2 (s), 130.9 (d), 124.9 (s), 122.3 (s), 115.2 (d), 74.4 (d), 70.8 (t), 62.4 (d), 38.4 (t), 31.6 (t); MS *m/z* 325 (M^+), 308 (54), 306 (56), 211 (7), 209 (7), 198 (13), 196 (14), 181 (12), 179 (11), 169 (7), 167 (7), 145 (0), 111 (100), 97 (96), 81 (34), 69 (27), 55(22); HRMS (CI^+) calcd for $C_{12}H_{12}O_4Cl_3$ (M+1) 324.9801. Found 324.9799.