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Stereocontrolled Functionalization of the Diene System of Compactin

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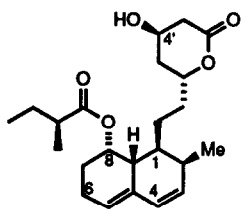
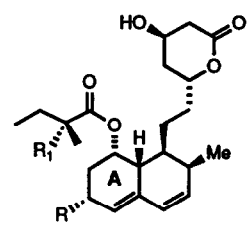
Abstract: *A facile regio- and stereoselective γ–functionlization of the 1,3-diene system of compactin via the key dienone 3 is described.*

Compactin (**1**),[1] mevinolin (**2a**)[2] and the related congener simvastatin (**2b**)[3] lower serum cholesterol levels in humans and thus provide important tools in the prevention and treatment of coronary artery disease.[4] Interestingly, the 6α-methyl group of mevinolin contributes 4-5 times more activity[5] as compared to compactin. In accordance with recently published work by H. Joshua et al.[6] and T-J. Lee et al.,[7] application of new methods for the functionalization of the 6 position of the compactin ring system have produced related congeners such as, **2c** which display a significantly higher activity than compactin. Therefore, development of an efficient method for direct introduction of alkyl groups at the C-6 position of compactin would provide an industrially feasible avenue to these and other potentially active analogues.[8] Disclosed herein is a mild entry for the activation of the C-6 position in the octalin unit via dienone **3** to provide regeoselective 1,3 γ–functionalization of the compactin-diene.



Compactin (1)

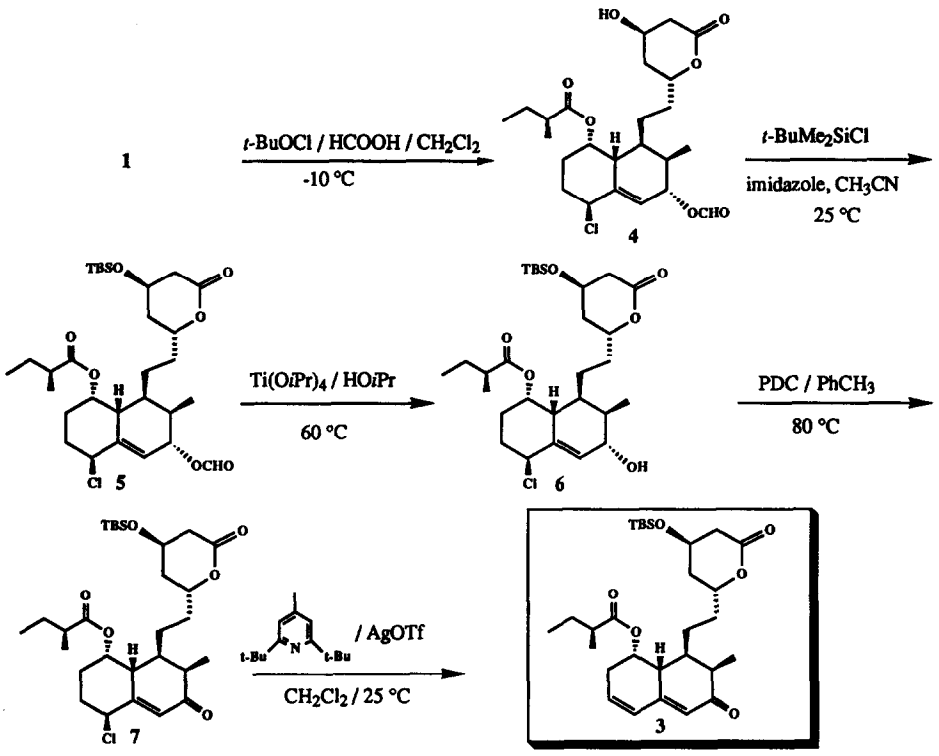


2a R = Me ; R_1 = H **(Mevinolin)**
2b R = Me ; R_1 = Me **(Simvastatin)**
2c R = α-CH_2OH ; R_1 = Me

The approach was based in the use of the long established 1,6-conjugate addition of nucleophiles to dienones which occurs with high stereoelectronic control.[9] In such a strategy, the sensitive dienone **3** which is properly positioned for 1,6-axial attack by carbon nucleophiles, becomes a key intermediate.[6] Thus development of an efficient transformation of the compactin-diene system into the dienone **3** (Scheme 1) and subsequent regeneration of the diene moiety with regiocontrol (Scheme 2) were key targets.

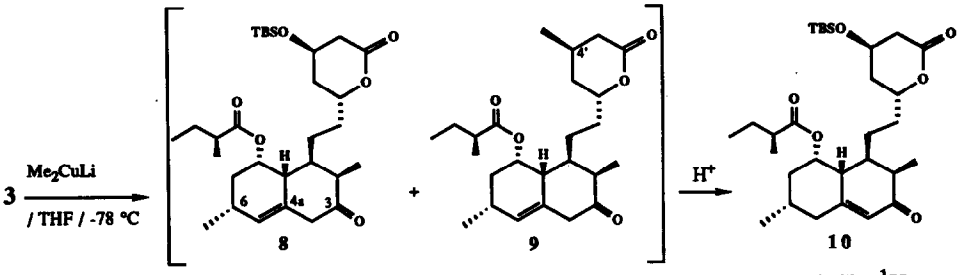
The dienone **3** was prepared from compactin (**1**) in five steps in 48% overall yield. Upon treatment with *one equiv* of *tert*-butylhypochlorite in a 1:1 mixture of formic acid and dichloromethane at -10°C, compactin underwent regio- and stereoselective 1,4-chloroformate formation to provide compound **4**.[10] Before further manipulation of the chloroformate, the sensitive 3-hydroxy-δ-lactone was protected as the TBDMS ether **5**. Due to the acid-labile silyloxy group, the potential for elimination at the $C_{4'}$ position in the presence of base, and

Scheme 1 SYNTHESIS OF DIENONE 3



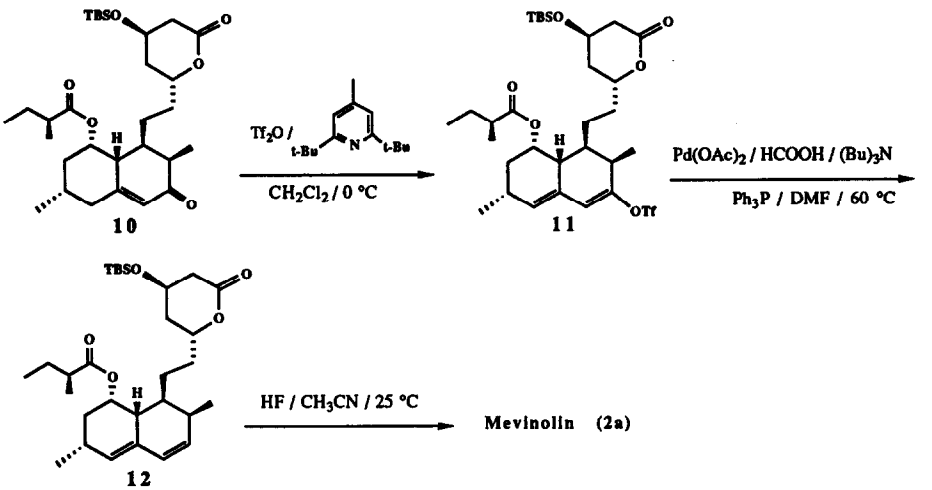
the C_8-acyloxy group, a mild, selective cleavage process for the formate group was required: Treatment of **5** with titanium isopropoxide in isopropanol at 60 °C for 30 min gave chemoselective transesterification[11] of the C_3 formate to produce chlorohydrin **6** in 68% overall yield from compactin. Oxidation of chlorohydrin **6** with PDC[12] in toluene at 80 °C for 20 min afforded chloroenone **7** in excellent yield (>92%). The elimination of the axial C_5-chloro substituent to prepare **3** was complicated by ring A aromatization and elimination of the C_4'-silyloxy moiety. These were avoided by reaction of chloroenone **7** with silver triflate and 2,6-di-*tert*-butyl-4-methylpyridine in dichloromethane at room temperature for one day to produce the key dienone **3** in 78% yield.[13]

Stereocontrolled cuprate addition took place according to precedent.[9] This was achieved by exposure of the dienone to 9.5 equiv of Me_2CuLi (MeLi/*freshly prepared* CuBr•Me_2S)[14] at -78 °C for 10 min to produce the desired, unstable 6-α-methyl-unconjugated enone **8** in 65% yield and undesired **9**; the latter product was obtained by elimination of the C_4'-silyloxy group of the lactone to form an α,β-unsaturated lactone with subsequent addition of methyl cuprate. The structure of compond **8** was confirmed as follows: The regiochemistry of the ketone, olefin and C_6 methyl was established with a COSY-2D experiment. The stereochemistry of the C_6-methyl was obtained indirectly from an NOE difference experiment whereby the H_8



proton was irradiated and the expected NOE enhancement to the 7-CH_2 was observed. The ^{1}H-spectral patterns for both H_7 protons were clearly defined in this experiment while in the 1D spectrum the equatorial H_7 proton was masked by other peaks. The coupling information obtained for the 7-CH_2 showed the expected large geminal splitting (J = 14.1 Hz); however, there was no diaxial coupling between the respective axial-H_7 and H_6 protons. These results are in agreement with the methyl group *alpha*-orientated at the C_6 postion.

Scheme 2 DIENE-REGENERATION



Regiospecific regeneration of the 1,3-diene system was efficiently accomplished in a two-step procedure (Scheme 2).[15] First, equilibration of the unconjugated enone **8** to the corresponding conjugated enone **10** occured easily on standing in acidic chloroform. This enone was then stirred with *freshly distilled* trifluoromethanesulfonic anhydride and di-2,6-*tert*-butyl-4-methylpyridine in dichloromethane at 0 °C for 15 min to give dienetriflate **11**. Without purification, this labile substance was exposed to palladium acetate, tributylamine, and formic acid in DMF at 60 °C for 1 h affording the desired *O*-TBS-mevinolin **12** in 70% yield.[16] Finally, the silyl protecting group was easily removed with 48% HF in acetonitrile at 25 °C for 1.4 h to provide mevinolin (**2a**) in 94% yield.

The synthetic material prepared by this route was identical with an authentic sample of mevinolin by ^{1}H NMR, ^{13}C NMR, TLC and DSC data. The key dienone intermediate **3** is anticipated to be extremely versatile for the synthesis of other C_6 analogues of compactin.

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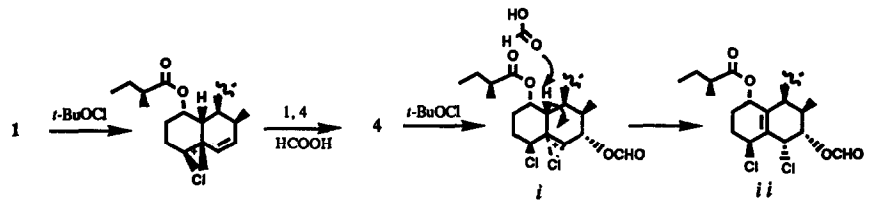
10. a) Reinholz, E.; Vogler, F. *Liebigs Ann. Chem.* **1987**, 1015. b) Formation of the chloroformate **4** is highly regio- and stereoselective. The regiochemistry of chlorine, olefin and formate groups was established from the COSY-2D experiment. The CH coupling (J = 157.4 Hz) at C_5 indicates the presence of a chloro group. The absence of a large diaxial coupling between H_6 and H_5 in the ^{1}H-NMR spectrum indicates H_5 is equatorial. The stereochemistry of the formate group is alpha based on NOE enhancement observed to H_1 when this group is irradiated. In this formate reaction 5% of impurity ***i*** was identified and characterized. Mechanistically, compound ***ii*** production can be explained as follows: after 1,4-additon of chloroformate across the diene unit the subsequent chlorination of **4** forms intermediate ***i***. Elimination then provides ***ii***. To prevent the second addition of chlorine it is critical to use one equiv of *tert*-butylhypochlorite . If two equiv were used, the main product was compound ***ii***.



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