Tetrahedron Letters 51 (2010) 57–59

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Conversion of pravastatin into an advanced intermediate for the synthesis of the HMG-CoA reductase inhibitor BB-476

J. J. Cronje Grove, Pieter S. van Heerden, Daneel Ferreira, Barend C. B. Bezuidenhoudt *

Department of Chemistry, University of the Free State, PO Box 339, Bloemfontein 9300, South Africa

ARTICLE INFO

Article history:
Received 21 July 2009
Revised 7 October 2009
Accepted 16 October 2009
Available online 22 October 2009

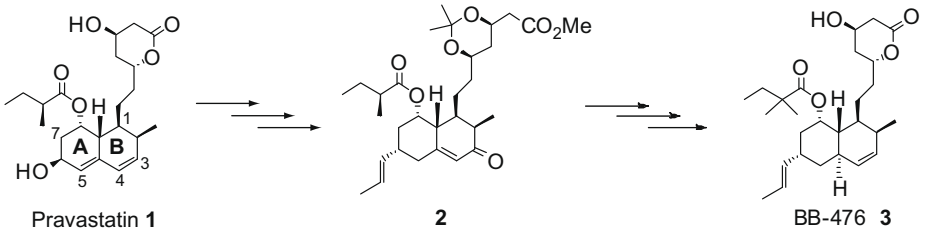
ABSTRACT

Rearrangement of the decalin system of pravastatin under S_N2' Mitsunobu conditions and subsequent selective hydrolysis and oxidation afforded a key dienone **23**, which upon copper-catalyzed addition of a 1*E*-propenyl moiety established the carbon framework of BB-476 **3** in high diastereomeric excess.

Inhibition of the enzyme HMG-CoA reductase, a rate-limiting step in the human de novo cholesterol biosynthesis pathway, has become an important therapeutic strategy in the management of atherosclerosis in humans.[1–3] Among the known inhibitors of HMG-CoA reductase,[4,5] one example with potential for clinical development is the mevinic acid analogue, BB-476 **3**. Owing to the many steps and low overall yield (ca. 2%) of the existing total synthesis[6] of BB-476 **3**, alternative routes for commercial access to this compound were investigated. The ready availability of pravastatin **1** from a fermentation process, prompted us to investigate a methodology involving the transformation of the pravastatin system into that of BB-476. Herein, we report a new protocol for the synthesis of a key intermediate **2** in the synthesis of BB-476.

The extremely acid-sensitive pravastatin **1** was isolated from a commercial source as the methyl ester **4**. Apart from converting the 8-*O*-(2*S*)-methylbutyryl group and the 1-(3,5-dihydroxyheptanoyl) side chain into 2,2-dimethylbutyryl and δ-lactone moieties, respectively, modification of the decalin unit in **4** requires substitution of the equatorial 6β-OH by an α-*E*-propenyl group and regio- and stereoselective reduction of the C4a–C5 double bond.

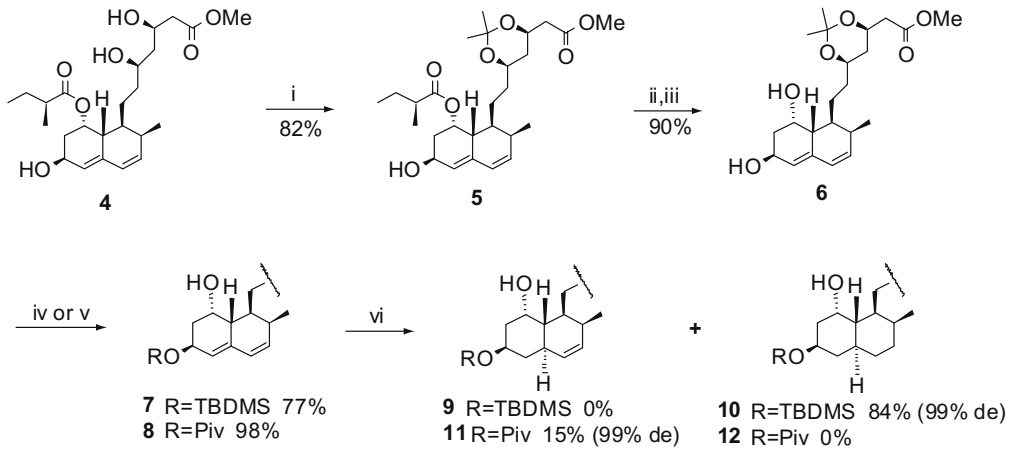
Protection of the 1,3-diol function of the side chain of the trihydroxy methyl ester **4** as the isopropylidene derivative **5**, a prerequisite for both substitution of the 6-OH group and reduction of the C4a–C5 double bond, proved to be problematic due to the extreme acid-sensitivity of pravastatin resulting in aromatization of its A-ring. Isopropylidene formation was eventually effected with 2,2-dimethoxypropane through application of the mild acidic catalyst pyridinium *p*-toluenesulfonate (PPTS)[7] in THF to afford the protected derivative **5** in 82% yield (Scheme 1). Saponification of the axial 8-(2-methylbutyryl) ester in **5** followed by acidification and methylation of the carboxylic acid functionality afforded diol **6** in 90% yield. Subsequent selective mono-silylation of the 6-OH group afforded the 8-hydroxy compound **7** as a substrate for selective reduction of the diene system. However, despite the literature precedent for the successful utilization of the Crabtree catalyst[8] for the reduction of mevinolin,[9] selective hydrogenation of the C4a–C5 olefinic bond in **7** was hampered by two major difficulties, that is, over-reduction to the fully saturated product **10** (ratio of **9**:**10** = 0:1) and/or inexplicable cessation of the reaction after a certain period of time.



Although electronic manipulation of the C4a–C5 double bond, via selective acylation of 6-OH as the pivaloyl ester **8**, increased the selectivity towards reduction (ratio of **11**:**12** = 1:0), the reaction was slow, and low conversion (15%) was observed after 24 h.

* Corresponding author. Tel.: +27 51 401 9021; fax: +27 51 444 6384.
E-mail address: bezuidbc.sci@ufs.ac.za (B.C.B. Bezuidenhoudt).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.080



Scheme 1. Reagents and conditions: (i) 2,2-dimethoxypropane, PPTS, THF, rt; (ii) NaOH (aq), MeOH, reflux, then $NaHSO_4$; (iii) CH_2N_2, −15 °C; (iv) $^tBuMe_2SiCl$, imidazole, THF, rt; (v) pivalic anhydride, pyridine, CH_2Cl_2, rt; (vi) $[Ir(COD)Py(PCy_3)]PF_6$, H_2, ^iPrOH, CH_2Cl_2, rt.

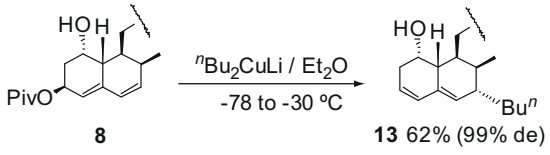
Attention was thus focussed on substitution of the 6β-hydroxy group with a carbon fragment prior to further attempts at hydrogenation of the diene system. Attempts at introducing the 6α-substituent by treatment of the pivaloyloxy group in **8** with the butyl Gillman cuprate reagent,[10] however, resulted in substitution exclusively via a 1,5-conjugative process leading to the 3α-alkylated product **13** (62%, 99% de) (Scheme 2). The regiochemical course of the reaction can be explained in terms of the relative inaccessibility of the C6–O σ^*-antibonding orbital, as well as the steric hindrance exercised by the axial C-8 hydroxy function.

In order to circumvent these problems, intramolecular displacement by transferring the carbon fragment from the 8α-OH to C-6, an approach that possesses the dual advantages of stereocontrol at C-6 and essentially no steric influence from the 8α-substituent, was next investigated. Thus, acylation of the mono-silylated methyl ester **7** with ethyl malonyl chloride followed by desilylation and acetylation afforded the di-acylated compound **16** in good overall yield (84%) (Scheme 3). Deprotonation of the malonate side chain of **16** with LDA (10% molar excess) at −78 °C, however, failed to give the desired lactone **17** via the anticipated intramolecular substitution. Such failure is attributable to conformational restrictions of the bulky C-8 ester group which was shown by molecular modeling calculations, to be preferentially directed away from the A-ring towards the side chain on the B-ring. In order to attain the required conformation for substitution, the potential of the electrostatic attractions operating in the Mitsunobu reaction[11] was subsequently investigated. Treatment of the hydroxy-ester **15** with DEAD/PPh_3 in dry benzene at 0 °C, however, again led to A-ring aromatization.

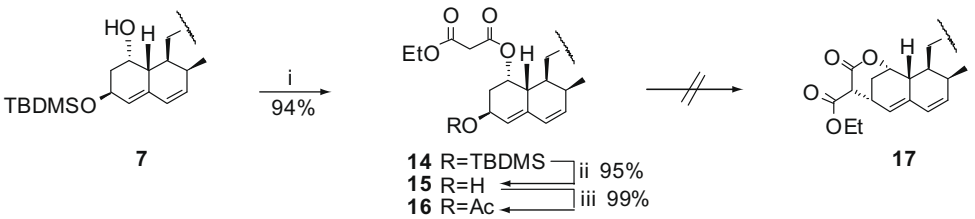
In a final attempt at intramolecular nucleophilic attack at C-6 of compound **16**, it was anticipated that a palladium species would be directed to the sterically less congested β-face of the allylic system.[12] Substitution of the *O*-acetyl moiety may then afford the target tricyclic lactone **17**. Efforts at inducing the transformation **16**→**17** using $Pd(PPh_3)_4$/NaH, failed invariably.

In order to overcome both the problems of A-ring aromatization and steric inaccessibility at C-6, we investigated methods for introducing the 6*E*-propenyl group via a double S_N2' reaction approach. Thus, application of Mitsunobu conditions[11] to compound **5**, afforded the 3α-benzoate ester **18** in 52% yield, and a mixture of epimers **19** and **20** in 16% and 26% yields, respectively. Formation of the benzoate ester **18** as the major product is promoted by the preference for an S_N2' pathway due to the hindered nature of the allylic system.[12] Selective saponification of the C-6 benzoate by-products **19** and **20** afforded epimerized starting material which was recycled. Selective hydrolysis of **18** afforded alcohol **21** and diol **22** in 75% and 9% yield, respectively. Subsequent PDC oxidation[13] of **21** yielded dienone **23** (87% yield), the key intermediate for introducing the propenyl group (Scheme 4). Copper-catalyzed addition[14] of 1-propenyl-magnesium bromide to the stereoelectronically preferred α-face at C-6[15] of **23** not only established the carbon framework **2** of BB-476 **3** in 66% yield,[16] but also circumvented the problems involving selective hydrogenation. The α-orientation of the C-6 propenyl substituent was confirmed by the observed NOE between the vinylic methyl group and the methyl groups of the 8-methylbutyryl side chain.

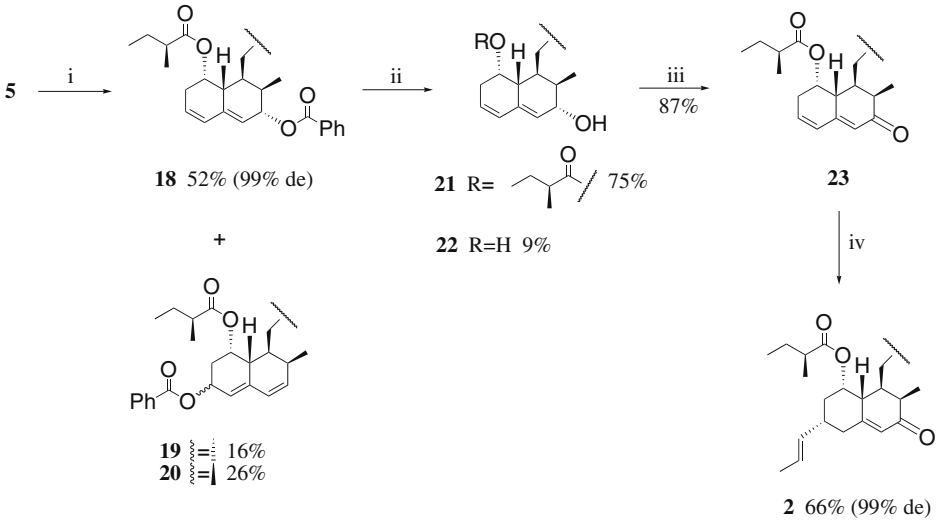
In conclusion, an efficient synthesis to establish the carbon backbone **2** of BB-476 **3** in five steps starting from readily available pravastatin **1** has been developed. Apart from a transesterification



Scheme 2.



Scheme 3. Reagents and conditions: (i) ethyl malonyl chloride, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) TBAF, THF, rt; (iii) Ac_2O, Py, 40 °C



Scheme 4. Reagents and conditions: (i) DEAD, PPh_3, $PhCO_2H$, THF, −78 °C; (ii) NaOMe, MeOH, rt; (iii) PDC, CH_2Cl_2, rt; (iv) CuI, (10 mol %), TMEDA, $CH_3CHCHMgBr$, THF, −25 °C.

step to attach the desired ester functionality at C8 and removal of the protecting group on the side chain, it only remains to introduce the B-ring double bond which should be possible through a trivial reductive elimination sequence. We have thus demonstrated the synthetic potential of this intermediate towards the total synthesis of BB-476.

Acknowledgements

Support by Bioclones (Pty) Ltd, Sandton, the Foundation of Research Development, Pretoria, and the 'Sentrale Navorsingsfonds' of this University is acknowledged.

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16. Characterization of **2**: HRMS $C_{29}H_{43}O_7$ requires *m*/*z* 503.3008. Found: *m*/*z* 503.3009 (M^+-CH_3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (1H, br s, H-4), 5.85 [1H, br s, H-4 (minor diastereomer)], 5.27–5.50 (3H, m, H-1″, H-2‴, H-8), 4.20–4.31 (1H, m, H-3′), 3.68–3.78 (1H, m, H-5′), 3.67 (3H, s, OCH_3), 2.60–2.70 (1H, m), 2.53 [1H, dd, *J* = 16.0, 7.0 Hz, H-2′(a)], 2.35 [1H, dd, *J* = 16.0, 6.0 Hz, H-2′(b)], 2.20–3.15 (4H, m), 1.90–2.00 (3H, m), 1.56 (3H, dd, *J* = 7.0, 2.0 Hz, 2‴-CH_3), 1.41 (3H, s, *iso*propylidene CH_3), 1.33 (3H, s, *iso*propylidene CH_3), 1.05 (3H, d, *J* = 7.0 Hz, 2″CH_3), 0.99 (3H, d, *J* = 7.5 Hz, 2-CH_3), 0.82 (3H, t, *J* = 7.5 Hz, 3″CH_3), 0.80–1.70 (9H, m). ν_{max} ($CHCl_3$) 1731, 1668, 1605, 1467 and 1386 cm^{-1}.