



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

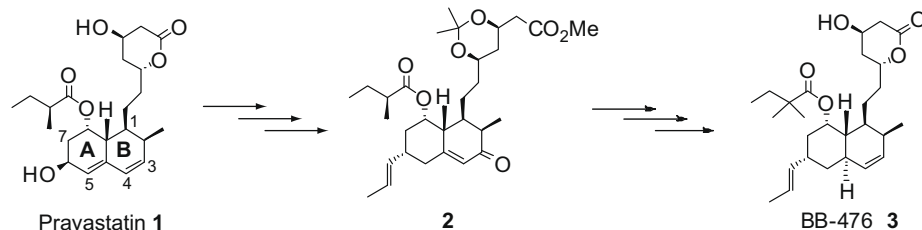
Rearrangement of the decalin system of pravastatin under S_N2' Mitsunobu conditions and subsequent selective hydrolysis and oxidation afforded a key dienone **23**, which upon copper-catalyzed addition of a 1*E*-propenyl moiety established the carbon framework of BB-476 **3** in high diastereomeric excess.

© 2009 Elsevier Ltd. All rights reserved.

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 synthesis⁶ 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.

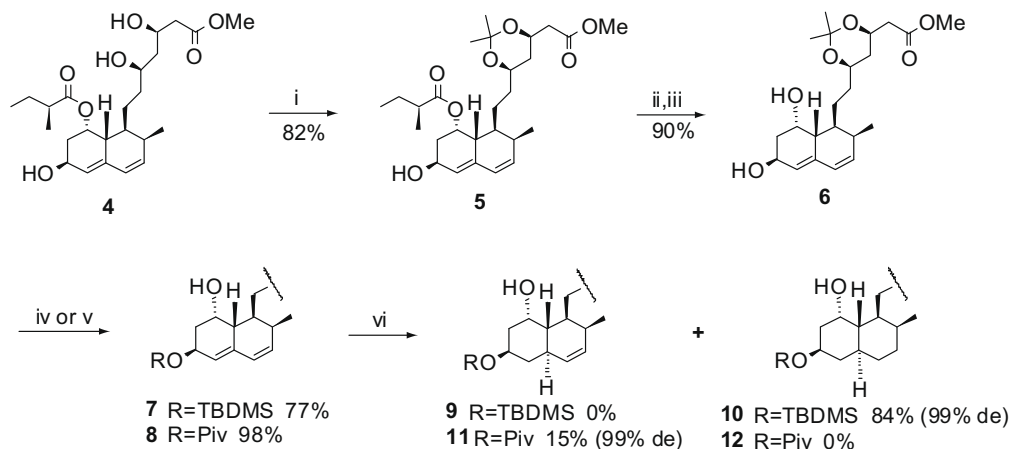
The extremely acid-sensitive pravastatin **1** was isolated from a commercial source as the methyl ester **4**. Apart from converting the 8-*O*-(2*S*)-methylbutyryl group and the 1-(3,5-dihydroxyheptanoyl) side chain into 2,2-dimethylbutyryl and δ -lactone moieties, respectively, modification of the decalin unit in **4** requires substitution of the equatorial 6 β -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 catalyst⁸ 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.

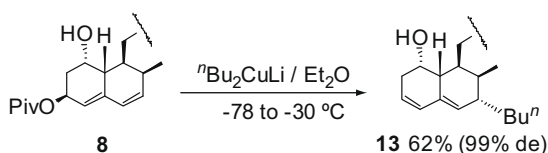
* Corresponding author. Tel.: +27 51 401 9021; fax: +27 51 444 6384.
E-mail address: bezuidbc.sci@ufs.ac.za (B.C.B. Bezuidenhoudt).



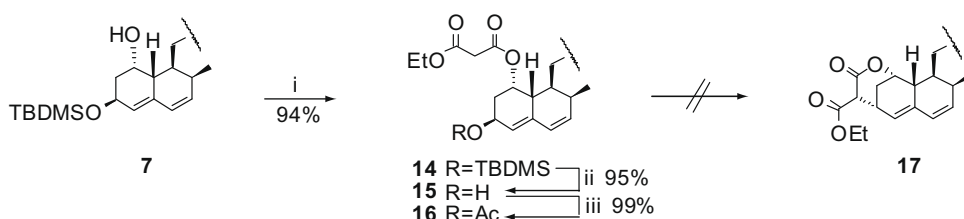
Scheme 1. Reagents and conditions: (i) 2,2-dimethoxypropane, PPTS, THF, rt; (ii) NaOH (aq), MeOH, reflux, then NaHSO₄; (iii) CH₂N₂, –15 °C; (iv) ^tBuMe₂SiCl, imidazole, THF, rt; (v) pivalic anhydride, pyridine, CH₂Cl₂, rt; (vi) [Ir(COD)Py(PCy₃)]PF₆, H₂, ^tPrOH, CH₂Cl₂, rt.

Attention was thus focussed on substitution of the 6 β -hydroxy group with a carbon fragment prior to further attempts at hydrogenation of the diene system. Attempts at introducing the 6 α -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 3 α -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 8 α -OH to C-6, an approach that possesses the dual advantages of stereocontrol at C-6 and essentially no steric influence from the 8 α -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 electro-



Scheme 2.



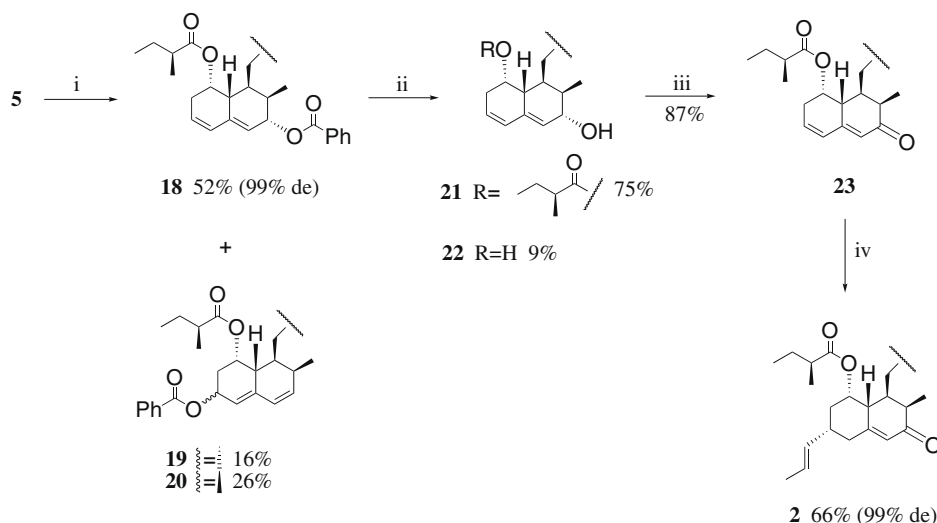
Scheme 3. Reagents and conditions: (i) ethyl malonyl chloride, 2,6-lutidine, CH₂Cl₂, 0 °C; (ii) TBAF, THF, rt; (iii) Ac₂O, Py, 40 °C

static attractions operating in the Mitsunobu reaction¹¹ was subsequently investigated. Treatment of the hydroxy-ester **15** with DEAD/PPh₃ 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(PPh₃)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 6E-propenyl group via a double S_N2' reaction approach. Thus, application of Mitsunobu conditions¹¹ to compound **5**, afforded the 3 α -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 oxidation¹³ of **21** yielded dienone **23** (87% yield), the key intermediate for introducing the propenyl group (Scheme 4). Copper-catalyzed addition¹⁴ of 1-propenyl-magnesium bromide to the stereoelectronically preferred α -face at C-6¹⁵ 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 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, $\text{CH}_3\text{CHCHMgBr}$, 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.

References and notes

1. Grundy, S. M. *West J. Med.* **1978**, 13, 128.
2. Daniewski, A. R.; Novkulich, P. M.; Uskovic, M. R. *J. Org. Chem.* **1992**, 57, 7133.
3. Erol, A. *Med. Hypotheses* **2005**, 64, 69.
4. Rádl, S.; Stach, J.; Hajicek, J. *Tetrahedron Lett.* **2002**, 43, 2087.
5. Arseniyadis, S.; Brondi-Alves, R.; Yashunsky, D. V.; Potier, P.; Toupet, L. *Tetrahedron* **1997**, 53, 1003.
6. Blackwell, C. M.; Davidson, A. H.; Launchburg, S. B.; Lewis, C. N.; Morrice, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, 57, 5596.
7. Fanton, G. J.; Horton, D. *J. Chem. Soc., Chem. Commun.* **1980**, 21.
8. Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, 51, 2655.
9. DeCamp, A. E.; Verhoeven, T. R.; Shinkai, I. *J. Org. Chem.* **1989**, 54, 3207.
10. Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, 95, 7777.
11. Mitsunobu, O. *Synthesis* **1981**, 1.
12. Trost, B. M. *Acc. Chem. Res.* **1980**, 11, 385.
13. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 5, 399.
14. Millar, J. G.; Underhill, E. W. *J. Org. Chem.* **1986**, 51, 4726.
15. Senanayake, C. H.; Bill, T. J.; DiMichele, L. M.; Chen, Y. C.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1993**, 34, 6021.
16. Characterization of **2**: HRMS $\text{C}_{29}\text{H}_{43}\text{O}_7$ requires m/z 503.3008. Found: m/z 503.3009 ($\text{M}^+ - \text{CH}_3$). ^1H 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, isopropylidene CH_3), 1.33 (3H, s, isopropylidene 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} .