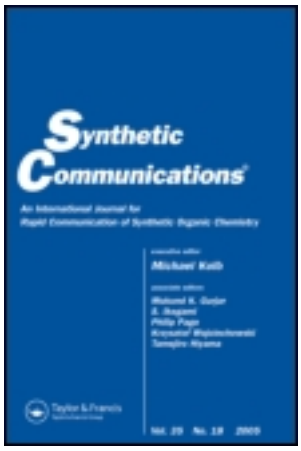

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A New Way to *tert*-Butyl [(4*R*,6*R*)-6-Aminoethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate, a Key Intermediate of Atorvastatin Synthesis

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ABSTRACT

A new synthesis of *tert*-butyl [(4*R*,6*R*)-6-aminoethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate, a key intermediate of the synthesis of an effective HMG-CoA reductase inhibitor atorvastatin, is described. The synthesis is based on the Henry reaction of nitromethane and *tert*-butyl [(4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate. The formed nitroaldol was then *O*-acetylated and the sodium borohydride reduction of the intermediate provided *tert*-butyl [(4*R*,6*R*)-2,2-dimethyl-6-nitroethyl-1,3-dioxan-4-yl] acetate. Catalytic hydrogenation of the nitro group led to the title compound.

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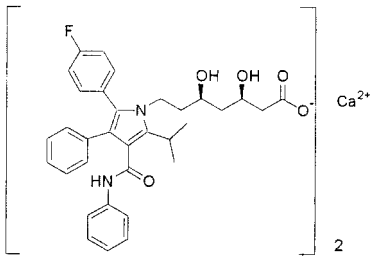
Key Words: Atorvastatin; Synthesis; Swern oxidation; Henry reaction.

Atorvastatin (**1**, Lipitor®, Sortis®) is a leading HMG-CoA reductase inhibitor on the market.[1] There are several efficient methods of synthesis of this drug, mostly based on the convergent synthesis using *tert*-butyl [(4*R*,6*R*)-6-aminoethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**2**) as a key intermediate. All the described methods of preparation of this intermediate are based on a catalytic reduction of *tert*-butyl [(4*R*,6*R*)-6-cyanomethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**3**).[2,3] The reduction should be done under elevated pressure and to prevent secondary amine formation, ethanolic ammonia is used as a solvent.



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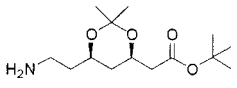

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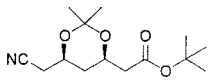
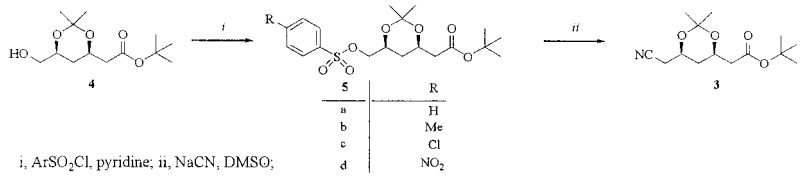
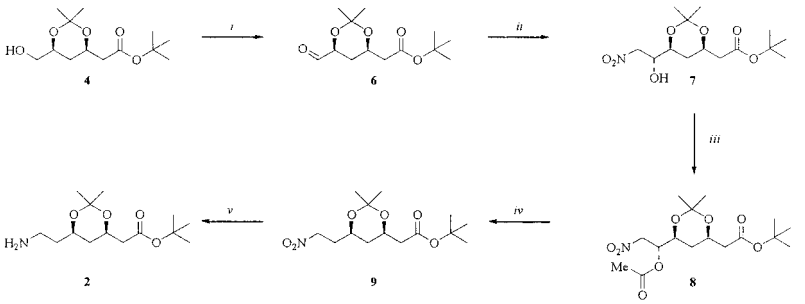


3

Several methods of preparation of the starting *tert*-butyl [(4*R*,6*R*)-6-cyanomethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate have been published and/or patented.[3–6] Our attention was given to *tert*-butyl [(4*R*,6*S*)-6-hydroxymethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**4**) having all the necessary steric features of atorvastatin. The compound has been prepared by several methods[7,8] and is also commercially available from Kaneka.[9] Brower et al.[2] used this compound for the synthesis of nitrile **3** by a method shown in Sch. 1. The methodology is based on the well-known carbon chain extension starting from the corresponding hydroxy derivative **4**. This compound was transferred to the corresponding benzenesulfonyl derivatives **5**. However, common benzenesulfonyl derivatives **5a** or **5b** were not enough reactive in the next step, i.e., in the reaction with sodium cyanide, under various conditions. Therefore more reactive 4-chlorobenzensulfonyl or 4-nitrobenzensulfonyl



Scheme 1.



Scheme 2.

derivatives **5c** or **5d** were used and the reaction times were still impractically long. No substantial improvement was achieved if the corresponding iodo derivative was used and the product was obtained in lower yields.[2]

Though the article[2] stated that the corresponding methanesulfonyl derivative was not reactive enough for the reaction with alkaline cyanides, we tried to use it for the reaction with tetrabutylammonium cyanide. However, the reactivity of the methanesulfonyl compound was found insufficient also under these conditions. Then we tried to use more reactive trifluoromethanesulfonyl derivative generated in situ and then treated with tetrabutylammonium cyanide, as it had been successfully used for similar systems.[10,11] Under the used conditions, we obtained a complex mixture containing less then 10% of the required nitrile (GC).

At the outset of our project we also decided to explore the possibility of using the hydroxy derivative as it is shown in Sch. 2.

The Swern oxidation of **4** leading to *tert*-butyl [(4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**6**) has been reported without any

details.[7] This compound can be also prepared from 2-propyl tartarate in several steps.[12] First we examined several modifications of the Swern reaction,[13,14] the classical setup using dimethyl sulfoxide activated by oxalyl chloride was found optimal giving repeatedly the required aldehyde **6** in about 70–80% yields. Though Wess et al. stated that the oxidation could not be done using chromium(VI)-based oxidants,[7] we succeeded in preparing the compound using pyridinium chlorochromate on alumina,[15] but the yields in a range of 45–55% were substantially lower than with the Swern method. Reaction of some aldehydes similar to **6**, e.g., 2,2-dimethyl-1,3-dioxolane-4-carbaldehyde, with nitromethane to give the corresponding nitroaldol (the Henry reaction) are well documented.[16,17] We found, that condensation of nitrometane with **6** using potassium fluoride in 2-propanol at room temperature, the conditions described by Wollenberg and Miller,[18] proceeded sufficiently well giving complete conversion after 5 h. The mixture, containing the corresponding nitroaldol as the only detectable product (TLC), after simple work-up provided **7** as a colorless, slowly solidifying oil. Though we were not particularly interested in studying the stereoselectivity of this reaction, it seems to be higher than for the similar Henry reaction of *(R)*-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde, where only moderate (80:20) stereoselectivity was reported.[17] In our case, the stereoselectivity seems to be higher since the sample obtained in high yield after one crystallization was shown to be pure one isomer of **7** (GC, ^{1}H NMR). Acylation of nitroaldols and the following reductive elimination is a well-known procedure using the Henry reaction products to the synthesis of simple nitroalkanes.[18,19] We acetylated crude nitroaldol **7** with acetic anhydride using DMAP as a catalyst. The reaction was sufficiently fast (r.t., 1 h) and simple elaboration provided high yield of pure **8** (GC purity higher than 99%). Reductive elimination of acetoxy group from **8** was done by sodium borohydride in ethanol at room temperature[18] to give from 85 to 92% yield of **9** as a colorless oil (98% GC purity). For patent protection reasons, also similar *O*-propionyl and *O*-butyryl analogs of **8** were prepared. Though their reductive elimination proceeded analogously to the acetyl derivative **8**, their use is not practical since the compounds were obtained as colorless oils and our attempts to get crystalline compounds failed. Methanolic solution of **9** was surprisingly smoothly catalytically hydrogenated at atmospheric pressure and room temperature using Raney nickel or Pd/C. Simple filtering and evaporation provided **2** as a colorless oily product in nearly quantitative yields (98% GC purity). Though the amine was reported[2] to be unstable, in our hands the compound was found stable enough to be stored at -30°C under argon for several weeks without appreciable decomposition (GC).

In conclusion, we have developed a new way of preparation of *tert*-butyl [(4*R*,6*R*)-6-aminoethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**2**) from *tert*-butyl [(4*R*,6*S*)-6-hydroxymethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**4**). All the reaction steps are simple, fast, and can be done at room temperature. The method provided the title compound in about 50–60% overall yield.

EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker instrument (250 MHz); chemical shifts are given in ppm (δ-scale). Infrared spectra (KBr) were recorded on a Perkin-Elmer FT-IR System Spectrum BX spectrometer, wavenumbers are given in cm^{-1}. Ultraviolet spectra were measured on a Shimadzu UV-260 spectrometer in ethanol, wavelengths are given in nm. Mass spectra were measured on a GC-MS instrument Finnigan MAT. The purity of the substances prepared was evaluated by TLC on silica gel (FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm.

***tert*-Butyl [(4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (6).** A solution of dimethyl sulfoxide (1.9 g, 22 mmol) in dichloromethane (5 mL) was added to a solution of oxalyl chloride (1.4 g, 11 mmol) in dichloromethane (20 mL) stirred at -50 to -60°C. Five minutes after the addition, a solution of **1** (2.6 g, 10 mmol) in dichloromethane (20 mL) was added during 10 min and the solution was stirred at -50°C for additional 30 min. Then triethylamine (8 mL) was added, the mixture was allowed to warm to room temperature during 2 h. Water (50 mL) was added and the mixture was extracted with dichloromethane; the combined extracts were washed with brine, dried with magnesium sulfate and evaporated. The residue was purified by flash chromatography (hexane–ethyl acetate, 9:1) to give 2.1 g of **6** (77%) as a colorless oil. ^{1}H NMR spectrum ($CDCl_3$): δ 1.24 (m, 1H), 1.40 (bs, 3H), 1.45 (bs, 3H), 1.52 (s, 9H), 1.84 (dt, J=3.2, 12.7 Hz, 1H), 2.40 (m, 2H), 4.35 (m, 2H), 9.58 (d, $J = 0.5$ Hz, 1H).

***tert*-Butyl [(4*R*,6*S*)-6-(1-hydroxy-2-nitroethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (7).** Nitromethane (5 mL) was added dropwise to a stirred mixture of *tert*-butyl [(4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**6**) (9.7 g, 37.6 mmol) and dry potassium fluoride (0.25 g) in 2-propanol (50 mL) and the mixture was stirred at room temperature for 5 h. Then the mixture was evaporated to dryness, the residue was dissolved in ether (250 mL), the insoluble portion was filtered through a Celite pad and the

filtrate was evaporated to give 11.4 g of white crystals (95%) of GC purity of 98.8%. Analytical sample was crystallized from a heptane-ether mixture giving white crystals, m.p. 129–137°C. Anal. calcd. for: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.37; H, 7.77; N, 4.41. $[\alpha]_D^{20} = +3.08°$. ^{1}H-NMR spectrum ($CDCl_3$): δ1.28 (dt, = 11.6, 12.7 Hz, 1H), 1.36 (bs, 3H), 1.43 (bs, 3H), 1.45 (s, 9H), 1.82 (dt, $J = 2.6$, 12.7 Hz, 1H), 2.33 (dd, $J = 6.0$, 15.2 Hz, 1H), 2.45 (dd, $J = 7.2$, 15.2 Hz, 1H), 2.81 (bs, 1H), 3.90 (ddd, $J = 2.6$, 6.6, 11.6 Hz, 1H), 4.13–4.33 (m, 2H), 4.45 (dd, $J = 8.5$, 13.5 Hz, 1H), 4.63 (dd, $J = 2.9$, 13.5 Hz, 1H). UV spectrum, λ_{max} (log ε): 207.2 (3.6). IR spectrum (KBr): 1556 (NO_2), 1722 [C-C(=O)-O], 3566 (OH).

***tert*-Butyl [(4*R*,6*S*)-6-(1-Acetoxy-2-nitroethyl)-2,2-dimethyl-1,3-dioxan-4-yl]-acetate (8). Method A.** Acetic anhydride (1.2 g) was added dropwise to a solution of **7** (3.2 g, 10 mmol) and 4-dimethylaminopyridine (0.05 g) in ether (50 mL) and the mixture was stirred at room temperature for 1 h. Then the solution was washed with brine and dried with magnesium sulfate. Evaporation of the filtrate provided 3.5 g of crude **7** of GC purity of 93%. Analytical sample was obtained by repeated crystallization from hexane giving white crystals, m.p. 92–95°C (GC purity of at least 99%). Anal. calcd. for: C, 53.18; H, 7.53; N, 3.88. Found: C, 52.96; H, 7.43; N, 3.72. ^{1}H NMR spectrum ($CDCl_3$): δ 1.32 (dt, $J = 11.4$, 12.8 Hz, 1H), 1.38 (bs, 3H), 1.41 (bs, 3H), 1.43 (s, 9H), 1.66 (dt, $J = 2.9$, 12.8 Hz, 1H), 2.02 (s, 3H), 2.30 (dd, $J = 6.0$, 15.2 Hz, 1H), 2.42 (dd, $J = 7.2$, 15.2 Hz, 1H), 4.03 (m, 1H), 4.18 (m, 1H), 4.68 (m, 2H), 5.28 (m, 1H). UV spectrum, λ_{max} (log ε): 206.0 (3.7). IR spectrum (KBr): 1228 [C-C(O)-C], 1560 (NO_2), 1724 [C-C(=O)-O], 1750 [C-C(=O)-O]. GC-MS, *m*/*e* (%): 290 (16), 248 (25), 230 (79), 188 (25), 170 (26), 139 (29), 81 (13), 59 (38), 57 (83), 43 (100), 41 (60), 39 (37).

Method B. Nitromethane (5 mL) was added dropwise to a stirred mixture of **6** (9.7 g, 37.6 mmol) and dry potassium fluoride (0.25 g) in 2-propanol (50 mL) and the mixture was stirred for 5 h at room temperature. Then the mixture was evaporated to dryness and the residue was dissolved in ether (250 mL). 4-Dimethylaminopyridine (0.1 g) and acetic anhydride (1.2 g) were added to the cloudy solution and the mixture was stirred at room temperature for 1 h. Work-up described in Method A then provided 12.1 g of crude **8** (GC purity of 93%).

***tert*-Butyl [(4*R*,6*R*)-2,2-dimethyl-6-(2-nitroethyl)-1,3-dioxan-4-yl]acetate (9).** A solution of **8** (12,1 g, 33.5 mmol) in ethanol (100 mL) was added dropwise to a stirred suspension of sodium borohydride (5 g) in ethanol (50 mL) with cooling in an ice bath and the mixture was stirred at room temperature for 1 h. Then the solution was poured into 10% solu-

tion of acetic acid (100 mL), the formed solution was extracted with ether, the extract was washed with brine and dried with magnesium sulfate. Evaporation of the filtrate provided 9.3 g of **9** (92%) as colorless oil of GC purity of 98%. $[\alpha]_D^{20} + 18.17^\circ$. ^{1}H NMR spectrum ($CDCl_3$): δ 1.22 (dt, J=11.4, 12.7 Hz, 1H), 1.34 (d, J=0.7 Hz, 3H), 1.42 (d, J=0.7 Hz, 3H), 1.44 (s, 9H), 1.61 (dt, J=2.5, 12.7 Hz, 1H), 2.02 (dddd, J=5.7, 8.1, 9.1, 14.6 Hz, 1H), 2.22 (dddd, J=3.3, 6.5, 7.1, 14.6 Hz, 1H), 2.30 (dd, J=6.1, 15.2 Hz, 1H), 2.42 (dd, J=7.0, 15.2 Hz, 1H), 3.96 (dddd, J=2.5, 3.3, 9.1, 11.4 Hz, 1H), 4.25 (dddd, J=2.5, 6.1, 7.0, 11.4 Hz, 2H), 4.45 (ddd, J=5.7, 7.0, 13.4 Hz, 1H), 4.54 (ddd, J=6.5, 8.1, 13.4 Hz, 1H). UV spectrum, λ_{max} (log ε): 205.8 (3.7). IR spectrum (KBr): 1554 (NO_2), 1721 [C-C(=O)-O].

***tert*-Butyl [(4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (2). Method A.** 10% Palladium on carbon (0.5 g) was added to a solution of **9** (3 g, 10 mmol) in methanol (50 mL) and the mixture was hydrogenated with stirring at room temperature without pressure till a hydrogen consumption was registered (about 2 h). The catalyst was filtered through a Celite pad, the filtrate was evaporated giving 0.3 g of **2** as a colorless oily product of GC purity of 98%. $[\alpha]_D^{20} = +13.12^\circ$. ^{1}H NMR spectrum ($CDCl_3$): δ 1.23 (m, 1H), 1.37 (s, 3H), 1.47 (s, 3H), 1.47 (s, 9H), 1.56 (m, 1H), 1.60 (m, 2H), 2.24 (bs, 2H), 2.30 (dd, J=6.0, 15.1 Hz, 1H), 2.43 (dd, J=7.0, 15.1 Hz, 1H), 2.85 (m, 2H), 3.99 (m, 1H), 4.26 (m, 1H). UV spectrum, λ_{max} (log ε): 204.2 (2.6). IR spectrum (KBr): 1721 [C-C(=O)-O], 3382 (NH_2). GC-MS: 274 (M + 1), 202 (M-CH_3–C_4H_8), 200 (M-OC_4H_9), 30 (CH_2NH_2).

Method B. The same setup using Raney nickel catalyst was used.

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REFERENCES

1. Graul, A.; Castaner, J. Atorvastatin. Drugs Fut. **1997**, *22*, 956–968.
2. Brower, P.L.; Butler, D.E.; Deering, C.F.; Le Tung, V.; Millar, A.; Nanninga, T.N.; Roth, B.D. The synthesis of (4R-*cis*)-1, 1-dimethylethyl-6-cyanomethyl-2, 2-dimethyl-1, 3-dioxane-4-acetate, a key intermediate for the preparation of CI-981, a highly potent, tissue

selective inhibitor of HMG-CoA reductase. Tetrahedron Lett. **1992**, *33* (17), 2279–2282.

3. Baumann, K.L; Butler, D.E.; Deering, C.F.; Mennen, K.E.; Millar, A.; Nanninga, T.N.; Palmer, C.W.; Roth, B.D. The convergent synthesis of CI-981, an optically active, highly potent, tissue selective inhibitor of HMG-CoA reductase. Tetrahedron Lett. **1992**, *33* (17), 2283–2284.
4. Butler, D.E.; Millar, A. Process for the Synthesis of (4R-*cis*)-1, 1-Dimethylethyl 6-cyanomethyl-2, 2-dimethyl-1, 3-dioxane-4-acetate. US Patent 5,103,024, April 07, 1992 (Warner-Lambert Co.).
5. Butler, D.E.; Le Tung, V.; Millar, A.; Nanninga, T.N. Process for the Synthesis of (5R)-1, 1-Dimethylethyl 6-cyano-5-hydroxy-3-oxo-hexanoate. US Patent 5,155,251, October 13, 1992 (Warner-Lambert Co.).
6. Mitsuda, M; Miyazaki, M.; Inoue, K. Process for producing 6-cyanomethyl-2-dimethyl-1, 3-dioxane-4-acetic acid derivatives. EP Appl. 1,077, 212 A1, April 28, **1999** (Kaneka Co.).
7. Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, H.; Schneirer, M. Stereoselective synthesis of HR 780, a new highly potent HMG-CoA reductase inhibitor. Tetrahedron Lett. **1990**, *31* (18), 2545–2548.
8. Beck, G.; Jendralla, H.; Kesseler K. Practical large scale synthesis of *tert*-butyl (3*R*,5*S*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxy-hexanoate: essential building block for HMG-CoA reductase inhibitors. Synthesis **1995**, 8, 1014–1018.
9. Nishiyama, A.; Horikawa, M.; Yasohara, Y.; Ueyama, N.; Inoue, K. Process for preparing optically active 2-[6-(hydroxymethyl)-1,3-dioxan-4-yl]acetic acid derivatives. WO 01/94,337, December 13, 2001 (Kaneka Co).
10. Masamune, S.; Ma, P.; Okumoto, H; Ellingboe, J.W.; Ito, Y. Synthesis of amphotericin B. 1. fragment A of the aglycon. J. Org. Chem. **1984**, *49* (15), 2834–2837.
11. de Raadt, A.; Griengl, H.; Klempier, N. A mild and simple enzymatic conversion of aldono- and alduruononitriles into the corresponding amides and/or carboxylic acids. J. Org. Chem. **1993**, *58* (11), 3179–3184.
12. Hiyama, T.; Minami, T.; Takahashi, K. Synthesis of artificial HMG-CoA reductase inhibitors based on the olefination strategy. Bull. Soc. Chem. Jpn. **1995**, *68* (1), 364–372.
13. Mancuso, A.J.; Swern, D. Activated dimethyl sulfoxide: useful reagents for synthesis. Synthesis **1981**, (3), 165–185.

14. Mancuso, A.J.; Huang, S.-L.; Swern, D. Oxidation of long-chain and related alcohols to carbonyls by dimethyl sulfoxide activated by oxalyl chloride. J. Org. Chem. **1978**, *43* (12), 2480–2482.
15. Cheng, Y.S.; Liu, W.-L.; Chen, S.H. Pyridinium chlorochromate adsorbed on alumina as a selective oxidant for primary and secondary alcohols. Synthesis **1980**, 3, 223–224.
16. Kozikowski, A.P.; Li, C.-S. A nitrile oxide based entry to 2,3-dihydropyran-4-ones. Synthesis of a protected version of "compactin lactone" in racemic and optically active forms. J. Org. Chem. **1985**, *50* (6), 778–785.
17. Kozikowski, A.P.; Kitagawa, Y.; Springer, J.P. An examination of the extent of diastereofacial selection in the reactions of a chiral nitrile oxide with achiral alkenes: a route to β-hydroxy carboxylic acids. J. Chem. Soc., Chem. Commun. **1983**, 23, 1460–1462.
18. Wollenberg, R.H.; Miller, S.J. Nitroalkane synthesis. A convenient method for aldehyde reductive nitromethylation. Tetrahedron Lett. **1978**, *19*, 3219–3222.
19. Schechter, H.; Ley, D.L.; Robertson, E.B. Nitroalkanes from conjugated nitroalkenes by reduction with complex hydrides. J. Am. Chem. Soc. **1956**, *78*, 4984–4991.

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