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An improved synthesis of 1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, a key intermediate for atorvastatin synthesis

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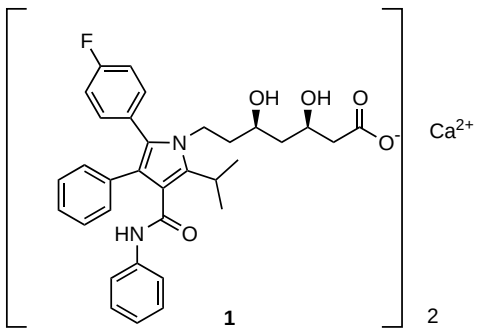
Abstract—An improved synthesis of 1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, a key intermediate for the synthesis of an effective HMG-CoA reductase inhibitor atorvastatin, is described. The synthesis is based on the iodolactonization of hepta-1,6-dien-4-ol to 4-allyl-6-iodomethyl-1,3-dioxan-2-one, which was converted in several steps to (6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)-acetonitrile. This intermediate provided (6-cyanomethyl-2,2-dimethyl-1,3-dioxan-4-yl)acetic acid either via the corresponding aldehyde or via (2,2-dimethyl-6-oxiranylmethyl-1,3-dioxan-4-yl)acetonitrile.

Atorvastatin (**1**, Lipitor®, Sortis®) is a synthetic lipid-lowering agent of great medicinal and commercial importance.[1] There are several efficient methods of synthesis, mostly based on the convergent synthesis using (4*R*,6*R*)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate **2** as a key intermediate.[2]

For analytical purposes we needed pure (3*S*,5*S*)-atorvastatin or its *cis*-racemate and therefore we decided to prepare (*cis*)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate or (4*S*,6*S*)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate.

Iodolactonization of unsaturated carboxylic esters has become a useful reaction for stereocontrolled introduction of chiral centers,[3] and subsequent conversion of the intermediate iodolactones into the corresponding epoxy derivatives is often used in the stereoselective synthesis.[4] Analogous stereocontrolled iodolactonization of allylic and homoallylic alcohols leading to the corresponding five- and six-membered cyclic iodocarbonates has been successfully used.[5] The iodocarbonates formed can be stereoselectively transformed to the corresponding epoxy alcohols.[5e,f,6] This strategy, starting from homoallylic alcohol **3**, was used in a patented method[7] of preparation of the *cis*-racemate of **2** shown in Scheme 1.

We started our synthetic efforts by repeating the patented procedure. However, we found that the procedure is not smoothly reproducible. The first isolated



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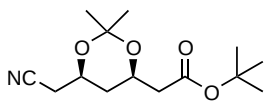

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Keywords: iodolactonization; stereocontrolled synthesis; atorvastatin intermediate.

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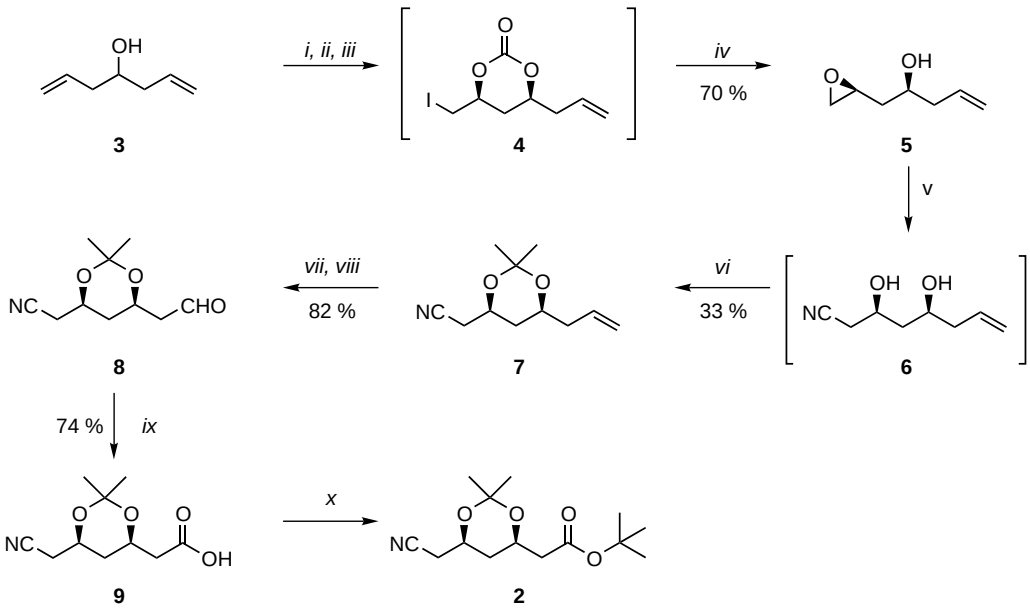
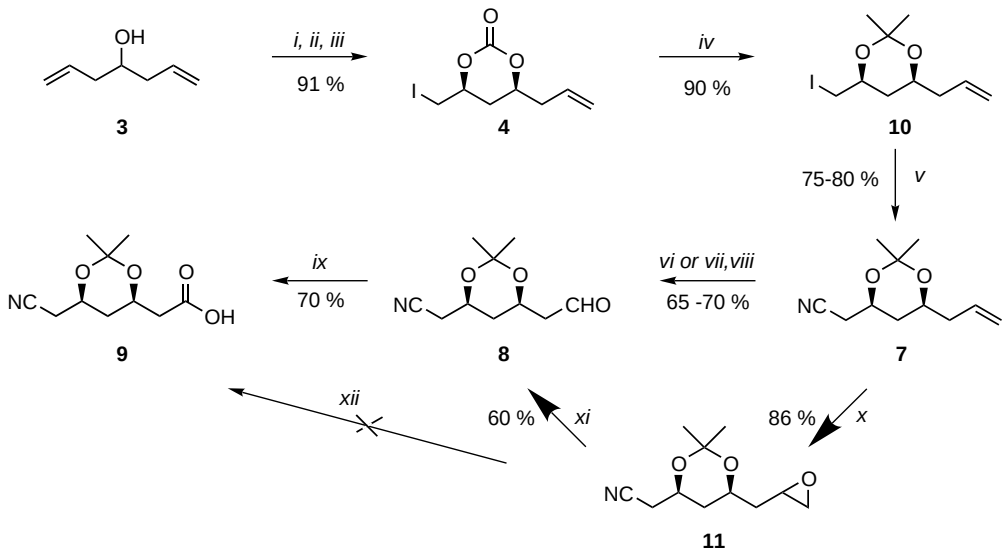


Scheme 1. (i) BuLi/THF; (ii) CO_2; (iii) I_2; (iv) K_2CO_3/MeOH–H_2O, rt; (v) KCN/*i*-PrOH–H_2O, rt; (vi) 2,2-dimethoxypropane; (vii) O_3; (viii) Ph_3P; (ix) CrO_3–H_2SO_4/acetone, 0°C; (x) *t*-BuOH, DCC, DMAP/CH_2Cl_2, rt.

intermediate described in the patent was epoxy alcohol **5**, which was obtained in 70% yield. In our hands, the yields were lower (50–60%) and, more importantly, the purity determined by GC was about 80%. The principal weakness of the procedure was the next step, i.e. treatment of the epoxide with KCN followed by ketalization with 2,2-dimethoxypropane, which provided nitrile **7** in only 33% yield. We repeated the procedure and obtained **7** in even lower yields and therefore we decided to modify the procedure as shown in Scheme 2.

The first iodolactonization step was carried out according to the well-established protocol. The intermediate iodolactone **4** was isolated and without purification treated with *p*-toluenesulfonic acid in dry acetone to provide **10** in about 90% yield. In the next step, the iodo derivative was treated with KCN in DMSO at 40°C for 125 h, giving nitrile **7** in 75–80% yield (overall yield at least 61%, compared to 23% claimed for the patented procedure[7]). The rest of the procedure leading to the *cis*-racemate **2** was easily reproducible, though the yields described in the patent were higher than those obtained by us. However, when higher quantities of **7** were used in the ozonization step, lower yields were obtained. A small improvement was achieved when triphenylphosphine was replaced with dimethylsulfide. We also tried using the well-known method using osmium(VIII) oxide–sodium periodate giving aldehyde **8** in about 65% yields. Oxidation of aldehyde **8** to the corresponding carboxylic acid was repeated



Scheme 2. (i) BuLi/THF; (ii) CO_2; (iii) I_2; (iv) *p*-TsOH, acetone, rt; (v) KCN/DMSO, 40°C; (vi) OsO_4–$NaIO_4$/dioxane–H_2O; (vii) O_3; (viii) Me_2S; (ix) CrO_3–H_2SO_4/acetone, 0°C; (x) *m*CPBA/CH_2Cl_2, rt; (xi) H_5IO_6/Et_2O, rt; (xii) CrO_3, H_5IO_6, acetone.

using Jones' reagent. Pyridinium chromate, as well as sodium chlorite, with or without a chlorine scavenger, was also used for the oxidation without apparent advantage. The last step, leading to the *cis*-racemate **2** was carried out according to the patented procedure with *tert*-BuOH, DCC, and DMAP.

Since we hoped, that this modification can also be used for production of larger amounts of the (4*R*,6*R*)-isomer of **2**, which serves as a key intermediate for atorvastatin synthesis, we tried to circumvent the potentially hazardous ozonization step. Compound **7** was smoothly oxidized with *m*CPBA to give satisfactory yields of epoxy derivative **11**. This compound could be hydrolyzed to the corresponding vicinal dihydroxy derivative, which should be easily oxidized to the corresponding aldehyde **8** with sodium periodate without the necessity to use highly toxic osmium(VIII) oxide.[8] We found that epoxy derivative **11** can be directly oxidized with periodic acid at room temperature by a slight modification of the published procedure[9] to yield aldehyde **8**. An attempt to prepare **9** by a direct oxidation of epoxy derivative **11** using chromium(VI) oxide and periodic acid in aqueous acetone at ambient temperature[10] failed.

In our attempts to obtain pure optical isomers of **2**, we prepared various salts of **9** with optically active amines, e.g. (*R*)-(+)-1-phenylethylamine, (*S*)-(−)-1-phenylethylamine, quinine and quinidine, and crystallized them from various solvents. The chiral purity of the recovered acid **9** was determined by HPLC on a cellulose tris(3,5-dimethylphenyl carbamate) chiral column, after the conversion to **2** as previously described.[11] However, none of these conditions led to a useful level of resolution.

The prepared compounds were characterized by ^{1}H,[12] ^{13}C NMR,[13] IR[14] and GC–MS.[15]

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12. ^{1}H NMR ($CDCl_3$); compound **2**: δ 4.28 dddd (J=2.5, 4.5, 7.6, 8.2 Hz), 1H [-CH(-O-)-]; 4.14 ddt, (J=1.6, 7.6 Hz), 1H [-CH(-O-)-]; 2.51 dd, (J=1.6, 7.6 Hz), 2H (CH_2CN); 2.47 dd (J=8.2, 14.2 Hz), 1H (CH_2C=O); 2.33 dd (J=2.5, 14.2 Hz), 1H (CH_2C=O); 1.75 dt (J=4.5, 7.6 Hz), 1H (CH_2); 1.46 s, 9H, (CH_3); 1.45 q (J=0.6 Hz), 3H (CH_3); 1.38 q (J=0.6 Hz), 3H (CH_3); 1.32 dt, 1H (CH_2). Compound **4**: δ 5.80 ddt (J=7.0, 9.8, 17.3 Hz), 1H (-CH=); 5.21 m, 2H (CH_2=); 4.54 ddt (J=3.1, 6.23, 12.0 Hz), 1H [-CH(-O-)-]; 4.46 dddd (J=3.1, 4.5, 6.9, 11.5 Hz), 1H [-CH(-O-)-]; 3.40 dd (J=4.5, 10.7 Hz), 1H (CH_2I); 3.30 dd (J=6.9, 10.7 Hz), 1H (CH_2I); 2.61–2.38 m, 2H (-CH_2-C=); 2.38 dt (J=3.1, 14.2 Hz), 1H (CH_2); 1.72 dt (J=12.0, 14.2 Hz), 1H (CH_2). Compound **7**: δ 5.79 dddd (J=6.5, 7.4, 10.3, 17.1 Hz), 1H (-CH=); 5. 10 dddt (J=1.3, 1.6, 2.2, 17.1 Hz), 1H (CH_2=); 5.08 dddt (J=1.0, 1.3, 2.2, 10.3 Hz), 1H (CH_2=); 4.11 ddt, (J=2.5, 6.0, 6.2 Hz), 1H [-CH(-O-)-]; 3.91 ddt, (J=2.5, 6.0, 6.6 Hz), 1H [-CH(-O-)-]; 2.54 dd (J=6.0, 16.6 Hz), 1H (CH_2CN); 2.46 dd (J=6.2, 16.6 Hz), 1H (CH_2CN); 2.33 ddddt (J=1.3, 1.6, 6.0, 6.5, 14.1 Hz), 1H (-CH_2-C=); 2.17 ddddt (J=1.0, 1.3, 6.6, 7.4, 14.1 Hz), 1H (-CH_2-C=); 1.68 dt (J=2.5, 12.8 Hz), 1H (CH_2); 1.26 dt (J=11.5, 12.8 Hz), 1H (CH_2); 1.45 q (J=0.7 Hz), 3H (CH_3); 1.40 q (J=0.7 Hz), 3H (CH_3). Compound **8**: δ 9.77 dd (J=1.5, 1.8 Hz), 1H (CH=O); 4.47 dddt (J=2.5, 5.9, 7.1, 11.7 Hz), 1H [-CH(-O-)-]; 4.18 dddt, (J=2.5, 5.9, 8.5, 11.7 Hz), 1H [-CH(-O-)-]; 2.65 dd, (J=7.1, 12.6 Hz), 1H (CH_2CN); 2.52 dd (J=5.9, 12.8 Hz), 1H (CH_2CN); 2.48 m, 2H (CH_2C=O); 1.76 dt (J=2.5, 12.6 Hz), 1H (CH_2); 1.48 q (J=0.5 Hz), 3H (CH_3); 1.39 q (J=0.5 Hz), 3H (CH_3); 1.16 dt (J=11.7, 12.6), 1H (CH_2). Compound **9**: δ 4.33 dddd (J=2.6, 4.5, 7.1, 8.2 Hz), 1H [-CH(-O-)-]; 4.20 ddt, (J=4.5, 6.0, 8.4 Hz), 1H [-CH(-O-)-]; 2.50 m, 2H (CH_2CN); 2.47 dd (J=8.2, 16.4 Hz), 1H (CH_2C=O); 2.33

dd (J=4.5, 16.4 Hz), 1H (CH_2C=O); 1.82 m, 1H (CH_2); 1.49 q (J=0.6 Hz), 3H (CH_3); 1.44 q (J=0.6 Hz), 3H (CH_3); 1.35 m, 1H (CH_2). Compound **10**: δ 5.80 dddd (J=6.3, 7.5, 10.2, 17.1 Hz), 1H (-CH=); 5.10 ddt (J=1.4, 2.2, 17.1 Hz), 1H (CH_2=); 5.07 ddt (J=1.2, 2.2, 10.2 Hz), 1H (CH_2=); 3.88 m, 1H [-CH(-O-)-]; 3.86 m, 1H [-CH(-O-)-]; 3.16 dd (J=5.9, 10.0 Hz), 1H (CH_2I); 3.08 dd (J=6.2, 10.0 Hz), 1H (CH_2I); 2.33 dtt (J=1.4, 6.3, 14.1 Hz), 1H (-CH_2-C=); 2.17 dddt (J=1.2, 6.4, 7.5, 14.1 Hz), 1H (-CH_2-C=); 1.80 dt (J=2.5, 12.8 Hz), 1H (CH_2); 1.10 dt (J=11.4, 12.8 Hz), 1H (CH_2); 1.43 q (J=0.7 Hz), 3H (CH_3); 1.41 q (J=0.7 Hz), 3H (CH_3). Compound **11**: δ 4.00–4.22 m, 2H [-CH(-O-)-]; 3.11 m, 1H (epoxide CH); 2.76 m, 1H (CH_2CN); 2.55 dd (J=2.8, 5.5 Hz), 2H (epoxide CH_2); 2.46m, 1H (CH_2CN); 1.75 m, 1H (CH_2); 1.67m 1H (CH_2); 1.48 q (J=0.6 Hz), 3H (CH_3); 1.45–1.26 m, 2H (CH_2); 1.40 q (J=0.6 Hz), 3H (CH_3).

13. ^{13}C NMR ($CDCl_3$); compound **2**: 172.94 (COOH); 117.45 (CN); 104.41 (-O-C-O-); 80.27 [$\underline{C}(CH_3)_3$]; 68.01 [-CH(-O-)-]; 66.71 [-CH(-O-)-]; 41.34 ($\underline{C}H_2$COOH); 40.96 (CH_2); 27.70 [$C(\underline{C}H_3)_3$]; 29.55 (CH_2CN); 24.91 (CH_3); 19.98 (CH_3). Compound **7**: 133.49 (-C=); 117.6 (CH_2=); 116.82 (CN); 99.23 (-O-C-O-); 68.05 [-CH(-O-)-]; 65.19 [-CH(-O-)-]; 40.46 ($\underline{C}H_2$-C=); 35.35 (-CH_2-); 29.78 (CH_3); 24.96 ($\underline{C}H_2$CN); 19.63 (CH_3). Compound **8**: 200.78 (CHO); 117.71 (CN); 105.24 (-O-C-O-); 66.35 [-CH(-O-)-]; 65.79 [-CH(-O-)-]; 50.34 ($\underline{C}H_2$CHO); 40.10 (-CH_2-); 26.07 ($\underline{C}H_2$CN); 24.91 (CH_3); 19.95 (CH_3). Compound **9**: 175.91 (COOH); 116.59 (CN); 99.66 (-O-C-O-); 65.56 [-CH(-O-)-]; 65.15 [-CH(-O-)-]; 40.77 ($\underline{C}H_2$COOH); 35.23 (-CH_2-); 29.63 ($\underline{C}H_2$CN); 24.86 (CH_3); 19.53 (CH_3). Compound **10**: 133.79 (-CH=); 117.30 (CH_2=); 99.31 (-O-C-O-); 68.53 [-CH(-O-)-]; 69.19 [-CH(-O-)-]; 40.50 ($\underline{C}H_2$CH=); 36.22 (-CH_2-); 29.91 (CH_3); 19.85 (CH_3), 9.44 (CH_2I). Compound **11**: 116.64 (CN); 99.08 (-O-C-O-); 66.29 [-CH(-O-)-]; 65.74 [-CH(-O-)-]; 51.93 (epoxide CH); 48.74 (epoxide CH_2); 39.29 (-CH_2-); 35.81 (-CH_2-); 29.55 ($\underline{C}H_2$CN); 24.91 (CH_3); 19.98 (CH_3).

14. IR ($CHCl_3$); compound **2**: 1725 (COO), 2255 (CN), 2820–2990 (CH, CH_2, CH_3). Compound **7**: 2259 (CN), 2820–3005 (CH, CH_2, CH_3). Compound **8**: 1729 (CHO), 2246 (CN), 2730–2990 (CH, CH_2, CH_3). Compound **9**: 1717 (COO), 2256 (CN), 2820–3010 (CH, CH_2, CH_3). Compound **11**: 2249 (CN), 2750–3010 (CH, CH_2, CH_3).

15. GC–MS, m/z (%); compound **2**: 254 (3), 198 (100), 154 (16), 138 (54), 120 (20), 59 (65), 57 (68), 43 (98), 41 (74), 39 (52), 28 (29). Compound **7**: 196 (17), 180 (50), 154 (51), 138 (19), 97 (21), 83 (100), 79 (74), 67 (23), 59 (33), 43 (56), 41 (19), 39 (53). Compound **10**: 283 (6), 282 (7), 281 (64), 221 (20), 197 (30), 169 (16), 93 (45), 79 (19), 67 (33), 59 (36), 43 (100), 41 (81), 39 (78), 28 (30).