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A NOVEL SYNTHETIC METHOD OF HMG-CoA REDUCTASE INHIBITOR NK-104 VIA A HYDROBORATION-CROSS COUPLING SEQUENCE

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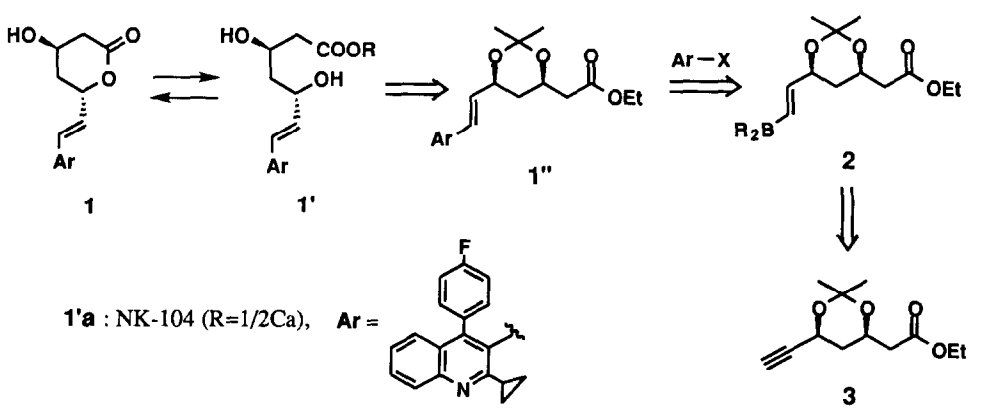
Abstract: The regioselective hydroboration of ethyl (*3R, 5S*)-3,5-isopropylidenedioxy-6-heptynoate, followed by the cross-coupling reaction with an aryl halide, provides ethyl (*3R, 5S, 6E*)-7-aryl-3,5-isopropylidenedioxy-6-heptenoate, a precursor of a highly potent HMG-CoA reductase inhibitor NK-104.

Compactin and mevalotin reported respectivly in 1976 and 1980 are potent inhibitors of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase.[1] These compounds consist of hexahydronaphthalene moiety and a key part mevalonic acid moiety. Accordingly, efforts have been made to replace the hexahydronaphtalene moiety by simple aromatic structures as type **1** or **1'**.[2] We independently have studied the structure-activity relationship of synthetic analogs and found NK-104 (**1'a**) is a highly potent HMG-CoA reductase inhibitor.[3] We wish to report here an alternatively convergent method for NK-104, whose retrosynthesis is shown in Scheme 1. Acetonide **1''**, a protected form of **1'**, would be prepared by the cross-coupling reaction[4,5] of an aryl halide or triflate with (*E*)-alkenyl borane **2** which can be derived from terminal acetylene **3** by hydroboration.

Scheme 1



We first studied the cross-coupling reaction of B-alkenyl-disiamylborane **2** obtained from racemic acetylene **3**[6] by hydroboration using 6 mol eq of disiamylborane followed by quenching the excess borane with basic ethanol. Representative conditions and results are summarized in Table 1. Sodium ethoxide (3 mol eq) as the base was more effective than Cs_2CO_3. After evaporation of the all volatile material, the residue was directly subjected to the cross-coupling reaction. Palladium(II) chloride or allylpalladium chloride catalyst gave higher yields of product than $Pd(PPh_3)_4$, probably because of the relatively slow rate of transmetalation reaction in the presence of Ph_3P ligand. After many screening experiments, we were pleased to find that treatment of Ar-I[7] with allylpalladium chloride in refluxing CH_3CN afforded **1"** in 99% yield.

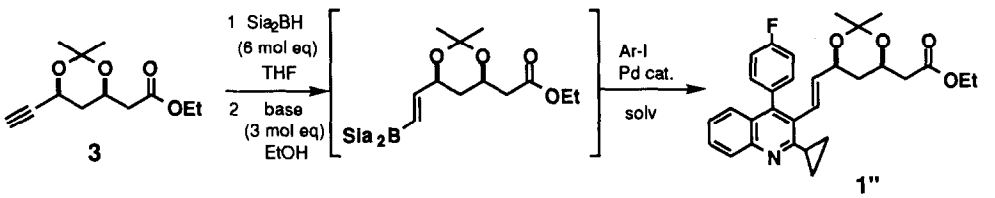


Table 1 Synthesis of **1"** by hydroboration of **3** followed by the cross-coupling.

run	catalyst	base	solvent	Yield(%)
1	$Pd(PPh_3)_4$	NaOEt	benzene	49
2	$Pd(PPh_3)_4$	Cs_2CO_3	THF	48
3	$Pd(PPh_3)_4$	NaOEt	THF	59
4	$(Ph_3P)_2PdCl_2$	NaOEt	THF	67
5	$Pd(OAc)_2$	NaOEt	THF	72
6	$(Allyl)_2Pd_2Cl_2$	NaOEt	THF	71
7	$(Allyl)_2Pd_2Cl_2$	NaOEt	DMF	88
8	$(Allyl)_2Pd_2Cl_2$	NaOEt	CH_3CN	99
9	$PdCl_2$	NaOEt	CH_3CN	97

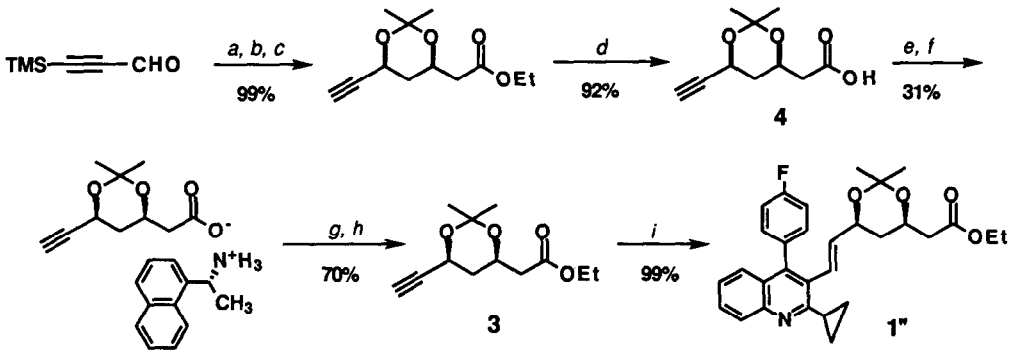
We also found that 9-BBN (2 mol eq) could be used instead of disiamylborane. Cross-coupling of the resulting B-alkenyl-9-BBN **2** (R_2B = 9-BBN) with Ar-I [1) NaOEt, EtOH; 2) $PdCl_2$ (10 mol %), CH_3CN] afforded **1"** in 93% yield. Catecholborane was found futile.

Triflate Ar-OTf was found to be another potent coupling partner.[8] Cross-coupling of **2** (R_2B = $(Sia)_2B$ or 9-BBN) with Ar-OTf in the presence of $PdCl_2$ in DMF gave **1"** in 90 or 70% yield, respectively.

We applied the present procedure to the synthesis of optically active NK-104 as shown in Scheme 2. Optically active acetylene **3** was obtained by resolution of racemic acid **4**. The carboxylic acid **4**, easily

prepared in 4 steps from 3-trimethylsilylpropynal, was transformed with (*R*)-(1-naphthyl)ethylamine to one of the diastereomeric salts which crystallized out in 31% yield. Esterification of the free carboxylic acid liberated from the crystalline salt gave the optically active acetylene **3** (97.3% ee).[9] This was converted into optically active **1"**[10] by the sequence of reactions described above in 99% yield.

Scheme 2



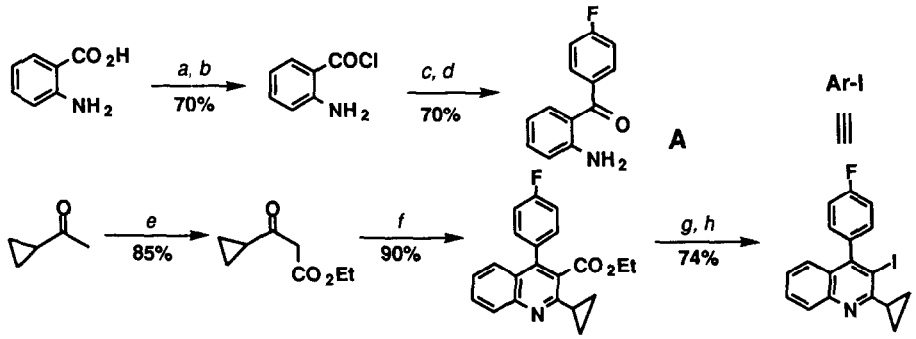
a: CH_2=C(OLi)CH=C(ONa)OEt, THF, -78°C, *b*: i) Et_2BOMe, ii) $NaBH_4$, *c*: 2,2-dimethoxypropane, TsOH, *d*: NaOH, *e*: (*R*)-naphthylethylamine, *f*: recrystallization, *g*: HCl, h: EtI, DBU, *i*: i) disiamylborane, ii) NaOEt, EtOH, iii) $PdCl_2$, Ar-I, CH_3CN

In summary, the strategy demonstrated herein for the synthesis of NK-104 allows us to combine the aryl moiety with the mevalonic acid moiety through the hydroboration-cross coupling reaction as the key steps. It is a great advantage of this strategy that various kinds of aryl part can be introduced at the last stage of synthesis. Accordingly, the present approach should be a useful methodology for the synthesis of a variety of HMG-CoA reductase inhibitors.

References and Notes

1. Review: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.
2. Connolly, P. *Chemtracts-Org. Chem.* **1992**, *5*, 59 and references cited therein.
3. a) Abstract of *XI International Symposium on Drugs Affecting Liquid Metabolism*, Florence, May 13-16, 1992 p22-23. See also b) Takano, S.; Kamikubo, T.; Sugihara, T.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *30*, 6051.
4. For some examples of the cross-coupling reaction of alkenylborane with aryl halides, see a) Miyaura, N.; Suzuki, A. *J. C. S. Chem. Comm*, **1979**, 866. b) Suzuki, A. *Pure Appl. Chem.*, **1985**, *57*, 1741. c) Miyaura, N.; Suzuki, A. *Yuki Gosei Kagaku Kyokaishi*, **1988**, *46*, 848.

5. Examples of the synthetic methods for HMG-CoA reductase inhibitors via cross-coupling are relatively few: a) Urabe, H.; Matsuka, T.; Sato, F. *Tetrahedron Lett.* **1992**, *33*, 4183. b) Takahashi, K.; Minami, T.; Ohara, Y.; Hiyama, T. *Tetrahedron Lett.* preceding paper. c) Sliskovic, D. R.; Blankley, D. J.; Krause, B. R.; Newton, R. S.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Sekerke, C.; Shaw, M. K.; Stanfield, R. L. *J. Med. Chem.* **1992**, *35*, 2095.
6. Racemic acetylene 3 was prepared according to Scheme 2 from 3-trimethylsilylpropynal by the sequence of reactions: (1) CH_2=C(OLi)CH=C(ONa)OEt, THF, -78 °C, 99%; (2) (i) Et_2BOMe (ii) $NaBH_4$; (iii) $Me_2C(OMe)_2$, TsOH, 92%; (3) *n*-Bu_4NF, THF, -78 °C, 74%, and showed ^{1}H-NMR (90MHz, $CDCl_3$): δ 1.26 (t, J = 7.3 Hz, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 1.5-2.0 (m, 2H), 2.2-2.7 (m, 3H), 4.15 (q, J = 7.3 Hz, 2H), 4.2-4.5 (m, 1H), 4.6-4.8 (m, 1H); IR (neat): 3250, 2100, 1720 cm^{-1}; MS: *m/z* 225 (M^+-1, 0.7), 211 (M^+-CH_3, 100), 197 (M^+-Et, 5.0).
7. Ar-I was prepared as follows.



a: TsCl, Na_2CO_3, H_2O, *b*: PCl_5, $ClCH_2CH_2Cl$, *c*: fluorobenzene, $AlCl_3$, $ClCH_2CH_2Cl$
d: H_2SO_4, *e*: $(EtO)_2CO$, *f*: **A**, PTS, *g*: KOH, dioxane-H_2O, *h*: I_2, hn, $PhI(OAc)_2$, CCl_4, reflux

8. Ar-OTf was prepared from cyclopropyl methyl ketone by the sequence of reactions: (1) Br_2, CH_3OH, 97%; (2) HCOONa, CH_3OH, reflux, 70%; (3) **A**, MsOH, benzene, reflux, and (4) Tf_2O, pyridine, 70% for steps (3) and (4).
9. The enantiomeric excess (ee) was determined by the capillary GC analysis (CP-Cyclodextrin-B-236M-19, 0.25 mm x 25m, Carrier gas He, Col. Temp. 100→190 °C, 4 °C/min).
10. ^{1}H-NMR (90MHz, $CDCl_3$): δ 0.9-1.1 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.4-1.5 (m, 1H), 1.6-1.7 (m, 1H), 2.34 (dd, J = 15.6 and 6.3 Hz, 1H), 2.42 (m, 1H), 2.52 (dd, J = 15.6 and 6.9 Hz, 1H), 4.17 (dq, J = 7.1 and 5.5 Hz, 2H), 4.2-4.3 (m, 1H), 4.3-4.4 (m, 1H), 5.58 (dd, J = 16.3 and 6.0 Hz, 1H), 6.55 (dd, J = 16.3 and 1.2 Hz, 1H), 7.1-7.4 (m, 6H), 7.5-7.6 (m, 1H), 7.9-8.0 (m, 1H); IR (neat) 1720, 1580, 1360, 960 cm^{-1}; MS: *m/z* 489 (M^+, 14.6), 442 (3.5) 288 (100); $[\alpha]_D^{20}$ +11.60 (*c* 1.00, $CHCl_3$).

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