Tetrahedron Letters, Vol.32, No.28, pp 3337-3340, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF δ-LACTONE, OXETANE AND AZETIDINONE ANALOGS FROM THE NATURALLY OCCURRING β-LACTONE L-659,699. THE PREPARATION OF A NOVEL HMG CoA SYNTHASE INHIBITOR.

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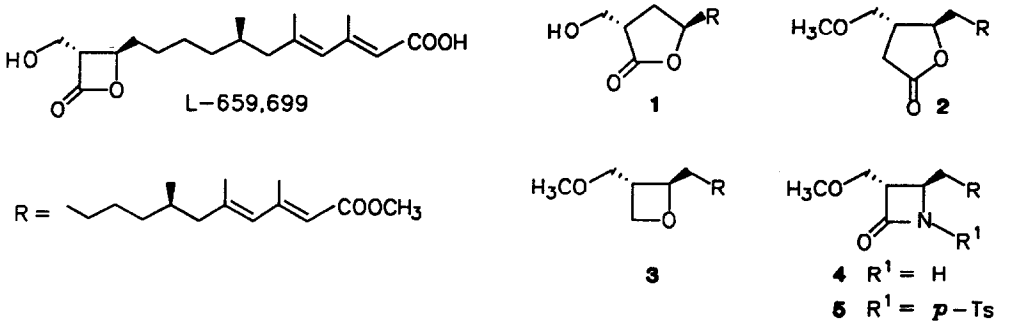
Summary: A series of δ-lactone (**1** and **2**), oxetane (**3**) and azetidinone (**4** and **5**) analogs were prepared from the HMG CoA synthase inhibitor L-659,699 ((E,E)-11-[3'R-(hydroxymethyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid[1,2]), which maintained the *trans* relationship of the ring side chains. The N-tosyl azetidinone analog represents the first reported member of a new series of non β-lactone HMG CoA synthase inhibitors.

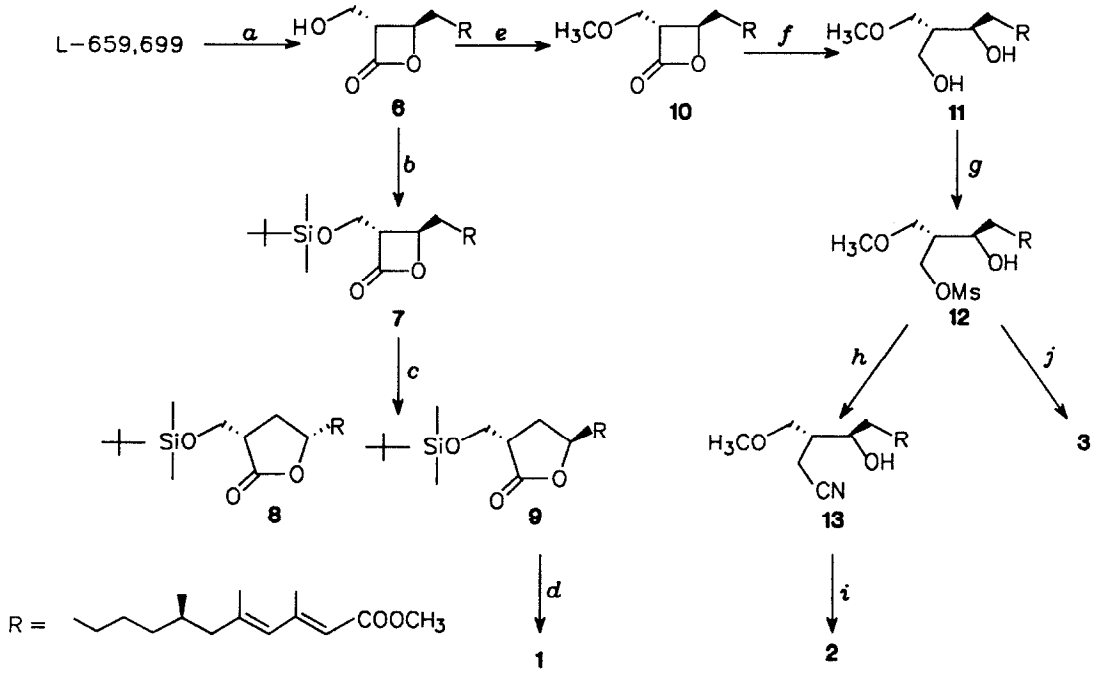
L-659,699 is a naturally occurring β-lactone, which has been independently isolated from *Cephalosporin* sp.[1], *Fusarium* sp.[3,4] and *Scopulariopsis* sp.[4]. The structure of L-659,699 was identified as (E,E)-11-[3'R-(hydroxymethyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid[1,2]. L-659,699 is a potent and specific inhibitor of partially purified 2-hydroxy-3-methylglutaryl-coenzyme A synthase (HMG-CoA synthase) isolated from rat liver (IC_{50} = 0.12 μM)[3]. L-659,699 also inhibited the incorporation of ^{14}C-acetate into cholesterol in human Hep G2 cells with an IC_{50} of 0.6 μM[3,4]. Studies suggest that the mechanism of enzyme inhibition by L-659,699 involves acylation of the β-lactone by a cysteine sulfhydryl or serine hydroxy on the enzyme[5-7]. Preliminary results indicate L-659,699 inhibits the enzyme irreversibly *in vitro*[6-8], but reversibly in cultured cells and animals[7]. To determine the effect of ring modification on enzyme inhibition, a series of δ-lactone (**1**,**2**,), oxetane (**3**) and azetidinone (**4**,**5**) analogs were prepared from L-659,699 (schemes 1). From this series, only the N-tosyl azetidinone (**5**) inhibited HMG CoA synthase (IC_{50} = 3.6 μM); all other compounds showed no activity up to 100 μM. Based on the mechanism of enzyme inhibition the activity of **5** can be attributed to the greater susceptibility of the N-tosyl azetidinone ring to nucleophilic attack relative to the other analogs. The N-tosyl azetidinone (**5**) represents the first reported member of a new series of non-β-lactone inhibitors of HMG CoA synthase.

Scheme 1



The preparation of the δ-lactones (**1** and **2**) is outlined in scheme 2. The methyl ester (**6**) of L-659,699 was obtained by treatment of L-659,699 with diazomethane. Protection of the C-3' hydroxymethyl group with *t*-butyldimethylsilyl chloride gave **7**. The concerted dyotropic rearrangement of **7** to a 1:2 *trans:cis* mixture[9] of the δ-lactones **8** and **9** was initiated by ethereal $MgBr_2$[10-13]. Removal of the silyl blocking group of **8** with tetra-*n*-butylammonium fluoride afforded **1**. The other δ-lactone analog of L-659,699 was prepared starting from the methyl ester (**6**) of L-659,699. The C-3' hydroxymethyl group of **6** was methylated with methyl iodide/silver oxide to give **10**, subsequent reduction with $NaBH_4$ afforded **11**. Selective mesylation of **11** gave the monomesylate **12**, which was displaced with cyanide to yield **13**. The cyano group of **13** was hydrolyzed and dehydrated to the δ-lactone **2** by heating **13** in the presence of HCl/MeOH. The oxetane analog (**3**) of L-659,699 was obtained by treating **12** with KOH/MeOH resulting in the displacement of the mesylate group by the C-2' hydroxy group (scheme 2).

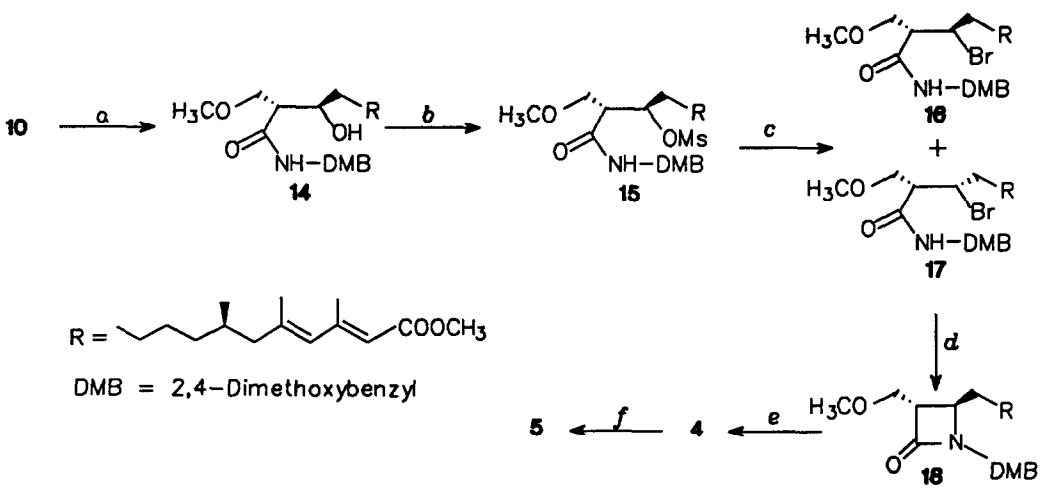
Scheme 2



(a) CH_2N_2, 22°C, 1 hr, 96%; (b) 2 equiv of t-butyldimethylsilyl chloride, 3.0 equiv of imidazole, DMF, 0°C, 1 hr, then 22°C, 1 hr, 71%; (c) 1.0 equiv magnesium bromide etherate, diethyl ether, 22°C, 16 hrs, 7% of a 1:2 mixture of 8:9[14]*; (d) 1.5 equiv tetrabutylammonium fluoride, HOAc-THF (1:5), 22°C, 2 hrs, 53%; (e) 5 equiv of Ag_2O, 20 equiv of CH_3I, 47°C, 5 hrs, 66%; (f) 20 equiv $NaBH_4$, MeOH, 22°C, 3 hrs, 18%; (g) 2.4 equiv MsCl, pyridine-CH_2Cl_2 (1:15), 22°C, 1 hr 50%; (h) 5 equiv of NaCN, DMF, 90-100°C, 2 hrs, 48%; (i) 12 N HCl-MeOH (1:20), 53°C, 3 hrs, 48%; (j) 6.0 equiv of KOH, MeOH, 50-55°C, 3 hrs, 50%.*

The azetidinones, **4** and **5**, were prepared as outlined in scheme 3. The β-lactone ring of **10** was opened by nucleophilic attack of 2,4-dimethoxybenzylamine at the ring carbonyl group to give **14**. Compound **14** was mesylated with methanesulfonyl chloride to give **15**. The mesylate group of **15** was then displaced with bromide with an inversion of configuration at C-2'. Some racemization was observed during the displacement and a 1:1.6 mixture of C-3'R (**16**) to the desired C-3'S (**17**) was isolated. The two diastereomers (**16** and **17**) were readily separated by chromatography. The intramolecular cyclization of **17** to **18** was effected by KOH, in the presence of the phase transfer reagent, tetra-*n*-butylammonium bromide[15], and proceeded with inversion of configuration at C-2'. Both the conversions of **15** to **17**, and **17** to **18** resulted in the inversion of configuration at C-2' to give a net retention of configuration at this position. The dimethoxybenzyl group (DMB) of **18** was oxidatively removed by ceric ammonium nitrate to give **4**. Tosylation of **4** with *p*-toluenesulfonyl chloride in the presence of tetra-*n*-butylammonium bromide and KOH gave **5**.

Scheme 3



(a) 3 equiv of 2,4-dimethoxybenzylamine·HCl, NEt_3-H_2O (7:1), 22°C, 1 hr, 50%; (b) 2.5 equiv of methanesulfonyl chloride, pyridine, 0°C, 2 hrs, 85%; (c) 1.0 equiv of NaBr, DMF, 100°C, 1 hr, 38% of a 1.6:1 mixture of 14:15; (d) 3.5 equiv of KOH, 0.12 equiv of tetrabutylammonium bromide, CH_2Cl_2-CH_3CN (19:1), 22°C, 16 hrs, 53%; (e) 2.3 equiv of $(NH_4)_2Ce(NO_3)_6$, H_2O-THF (1:1), 22°C, 1.5 hrs, 65%; (f) p-tolylsulfonyl chloride.

Acknowledgement: We wish to thank Mr. Jack L. Smith for the mass spectral analysis, and Dr. James V. Heck for his advice on the preparation of the manuscript.

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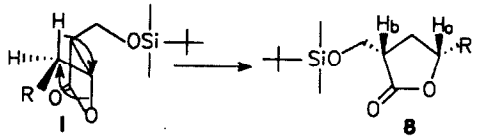
(9) The *cis* and *trans* isomers were separated on silica gel eluted with 1:5 ethyl acetate:hexane. The preferential formation of the *cis* substituted δ-lactone (**8**) was probably the result of steric factors in the transition state. The lower energy transition state with the C-2' side chain oriented away from the β-lactone ring (I) would lead to the *cis* product (**8**), while the transition state with the side chain eclipsing the ring (II) would give the *trans* product (**9**). The assignment of *cis* and *trans* was based on NOE differences in the two isomers. Irradiation of Ha elicited an NOE signal from Hb in **8** indicating the protons were *cis*, while no signal was observed for Hb in **9** indicating the protons were *trans*.



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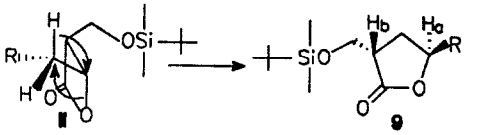

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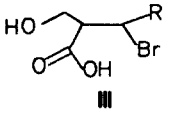
(14) The δ-lactones were prepared in only a 7% yield. The major product was the ring opened bromo acid III (50%). Running the reaction at 0°C or reflux did not improve the yield. The use of $MgBr_2$ in THF or substituting *t*-butyldimethylsilyl trifluoromethanesulfonate for $MgBr_2$ failed to produced any δ-lactone products.



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(Received in USA 17 December 1990)