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Degradation of the C1 Side Chain of Zaragozic Acid A

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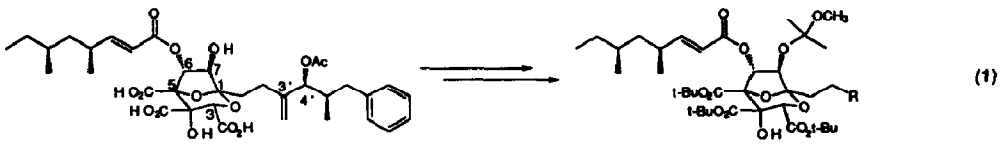
Abstract: *A chemoselective degradation of the C1 sidechain of the natural product squalene synthase inhibitor zaragozic acid A (1) is described. Key to this degradation sequence is the selective ozonolysis of the C3' olefin. The degraded sidechain provides convenient intermediates for additional synthetic studies with this class of natural products.*

The lowering of serum cholesterol levels by the inhibition of HMG-CoA reductase (EC 1.1.1.34) has been an effective therapy for reducing the risks of heart disease.[1] Recently, the inhibition of cholesterol biosynthesis has been investigated via the directed substrate inhibition of the enzyme squalene synthase (EC 2.5.1.21).[2] This enzyme catalyzes the head-to-head condensation of two molecules of farnesyl pyrophosphate to form presqualene pyrophosphate. As the first committed step in the synthesis of sterols, this should be an effective point for the inhibition of cholesterol production.[3] Extensive screening efforts have recently led to the isolation of zaragozic acid A (**1**), a natural product that is a potent inhibitor of squalene synthase.[4] In an effort to explore the unique chemistry and cholesterol lowering effects of **1**, a study was undertaken to investigate changes in the functionality of the C1 alkyl side chain. An efficient and selective degradation of the C1 alkyl side chain was required that would produce versatile intermediates to construct semisynthetic derivatives[5] (Equation 1). In this Letter the oxidative degradation of the C1 side chain of zaragozic acid A (**1**) is detailed.



Zaragozic Acid A (1)

2, R = CHO
3, R = CH_2OH
4, R = CO_2H

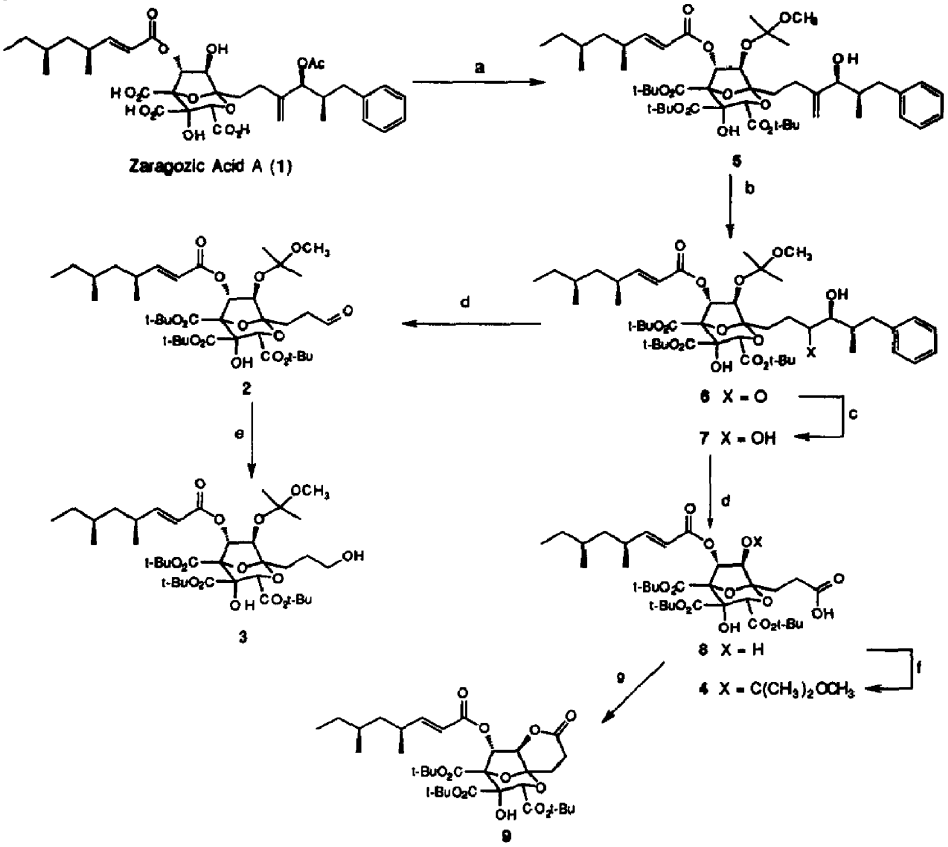
(1)

Allylic alcohol **5**[6] (Scheme 1) was prepared in 3 steps from zaragozic acid A (**1**) in an overall yield of 85%. Numerous methodologies were investigated for the selective oxidation of this methylidene group in preference to the α,β-unsaturation of the fatty acyl side-chain without success. The most successful of these involved the use of stoichiometric osmium tetroxide, which was effective only when C7 was unprotected.[7] Ozonolysis of the C3' olefin under standard conditions or in the presence of the diazo indicator Sudan III gave complex reaction mixtures resulting from concomitant oxidation of the C6 ester side chain. Studies by Slomp[8] in the late 1950's demonstrated that the reactivity of ozone could be attenuated by addition of pyridine. Selective ozonolysis of the C3' olefin of **5** (O_3, CH_2Cl_2:pyridine, 40:1, -78°C) gave the α-hydroxy ketone **6** in 55% yield after silica gel chromatography.[9] Borohydride reduction of **6** gave the vicinal diol **7** as a 2:1 ratio mixture of

epimeric alcohols which was carried on without separation (95%). Oxidative cleavage of **7** with 1.1 equivalents of sodium metaperiodate in aqueous dioxane gave aldehyde **2** (84%).[10] Reduction of **2** ($NaBH_4$, CH_3OH) gave the alcohol (**3**) in 80% yield. Alternatively, treatment of **6** with excess sodium metaperiodate gave carboxylic acid **8** in which C7 2-methylmethoxyethyl protecting group had been hydrolytically cleaved.

To facilitate the synthesis of compounds derived from the C1 carboxylic acid **8**, the C7 protecting group was reintroduced by the following sequence: (1) esterification of the carboxylic acid **8** (BnBr, CH_3CN, DBU, reflux), (2) ketal formation (2-methoxypropene, *p*-PTS, CH_2Cl_2) and (3) debenzylation (10% Pd/C, 2,5-dihydrotoluene, CH_3OH, 45°C) gave the carboxylic acid **4** in 70% overall yield. This protection sequence was required in order to prevent the formation of lactone **9** upon activation of the carboxylic acid **8**. The sequence outlined above provided multigram quantities of each of the degradation intermediates of zaragozic acid A (**1**).

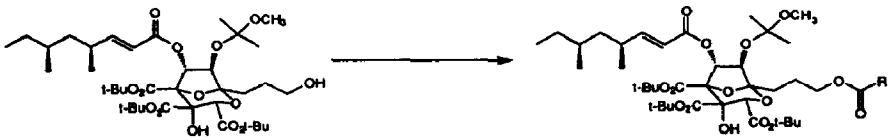
Scheme 1



Reagents (a) see reference 6; (b) i. O_3, CH_2Cl_2:pyridine (40:1), -78°C; ii. DMS, -78°C to r.t.; (c) $NaBH_4$, CH_3OH; (d) $NaIO_4$, dioxane, H_2O; (e) $NaBH_4$, CH_3OH; (f) i. benzyl bromide, DBU, CH_3CN, reflux; ii. 2-methoxypropene, *p*-PTS, CH_2Cl_2; iii. 10% Pd/C, dihydrotoluene, CH_3OH, 45°C; (g) DCC, DMAP, CH_2Cl_2.

Intermediates **3** and **4** could be derivatized using a varitey of standard reaction conditions as outlined in Equations 2 and 3. Acylation of alcohol **3** could be effected with DCC, DMAP and 3-phenylpropanoic acid to

give the ester (**10**) in 81% yield (Equation 2). Alternatively, acylation of **3** with either methyl or phenyl isocyanate gave the carbamates **11** and **12** in 89% and 84% yield, respectively.

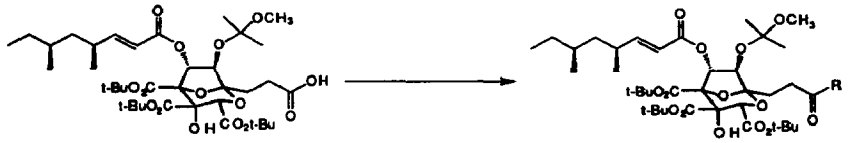


3

10, R = $(CH_2)_3Ph$
11, R = $NHCH_3$
12, R = NHPh

(2)

Treatment of the carboxylic acid **4** with phenethyl mercaptan, 4-phenylbutylamine and 4-phenyl-1-butanol gave thioester **13** (67%), amide **14** (63%) and ester **15** (36%), respectively.



4

13, R = $S(CH_2)_2Ph$
14, R = $NH(CH_2)_4Ph$
15, R = $O(CH_2)_4Ph$

(3)

The chemistry described in this Letter, coupled with our previous communication on the deacylation of the C6 ester[6] side chain of **1**, enables a convenient, high yielding, and selective degradation of the alkyl arms of the potent squalene synthase inhibitor zaragozic acid A (**1**).

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9. Experimental and spectral data for the synthesis of α-hydroxy ketone **6** are detailed: To a -78°C solution of the allylic alcohol **5** (500 mg, 0.56 mmol) in CH_2Cl_2:pyridine (20 ml of a 40:1 solution) was *slowly* bubbled ozone until TLC indicated the disappearance of the starting allylic alcohol **5** ($R_{f(5)}$ = 0.35 ; $R_{f(6)}$ = 0.45, 3:1 hexanes EtOAc). Upon complete consumption of the starting material the reaction was quenched with dimethylsulphide (10 mL) and allowed to warm to room temperature. The mixture was then concentrated *in vacuo* and chromatographed (silica gel, 4:1 hexanes:EtOAc to 100% EtOAc) to yield 275 mg (55%) of the α-hydroxyketone **6**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.28-7.17 (5H), 6.86 (dd, J=15.7, 8.2 Hz; 1H), 5.27 (s, 1H), 5.02 (s, 1H), 4.18 (m, 2H), 4.05 (s, 1H), 3.56 (d, J=4.1 Hz, 1H), 3.23 (s, 3H), 2.95 (m, 1H), 2.87-2.79 (m, 2H), 2.62 (dd, J=13.2, 7.7 Hz, 1H), 2.38-2.32 (m, 3H), 2.06-2.02 (m, 1H), 1.65 (s, 9H), 1.42 (s, 9H), 1.35 (s, 3H), 1.34 (s, 9H), 1.31-1.28 (m, 2H), 1.25 (s, 3H), 1.08-1.03 (m, 2H), 0.97 (d, J=6.7 Hz, 3H), 0.81-0.78 (m, 6H), 0.68 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 212.63, 169.03, 166.10, 164.49, 163.81, 156.74, 140.34, 129.40, 128.29, 126.02, 118.62, 103.67, 101.38, 90.61, 86.16, 84.29, 83.25, 80.69, 78.51, 76.69, 75.52, 73.67, 49.87, 43.19, 40.32, 38.01, 34.30, 31.77, 30.69, 29.61, 28.07, 28.02, 27.96, 27.84, 25.89, 24.48, 20.03, 18.84, 12.65, 11.07 ppm; MS FAB (negitive ion), m/e 833.5 [M-t-Bu], 719.6 [M-3(t-Bu)].

10. Spectral data for aldehyde **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (app. s, 1H), 6.86 (dd, J=15.7, 8.1 Hz, 1H), 6.41 (d, J=1.4 Hz, 1H), 5.73 (d, J=15.8 Hz, 1H), 5.03 (s, 1H), 4.21 (d, J=1.4 Hz, 1H), 4.03 (s, 1H), 3.23 (s, 3H), 3.05-2.98 (m, 1H), 2.85-2.77 (m, 1H), 2.42-2.33 (m, 2H), 2.15-2.05 (m,1H), 1.65 (s, 9H), 1.44 (s, 9H), 1.39-1.21 (m,3H), 1.36 (s, 3H), 1.35 s, 9H), 1.26 (s, 3H),1.10-1.01 (m, 2H), 0.97 (d, J=6.6 Hz, 3H), 0.86-0.78 (m, 7H); MS FAB (positive ion) m/e 903.2 (MH^++ Li+$HSCH_2CH(OH)CH(OH)CH_2SH$)

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