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The Asymmetric Syntheses of the C-1 Sidechains of Zaragozic Acid A and Zaragozic Acid C

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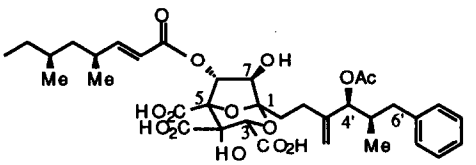
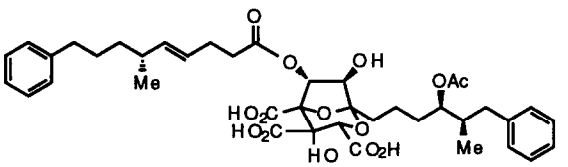
Abstract: The asymmetric syntheses of the C-1 sidechains of zaragozic acid A and C are described. Aldol reaction defines the chirality at C-4' and C-5' in two independent routes. Multigram preparation as well as a route amenable to derivatization are highlights of these approaches.

The recent isolation of a class of potent squalene synthase inhibitors, the zaragozic acids,[1] has been followed by extensive synthetic and biological studies.[2] With interests in total synthesis of these natural products as well as the synthesis of semisynthetic analogs, practical routes to the C-1 sidechains were desired. Important was introduction of a variety of functional attachments to allow convergence with these strategies. In this communication, syntheses of the zaragozic acid A and C sidechains are presented.



Zaragozic Acid A
L-694,599

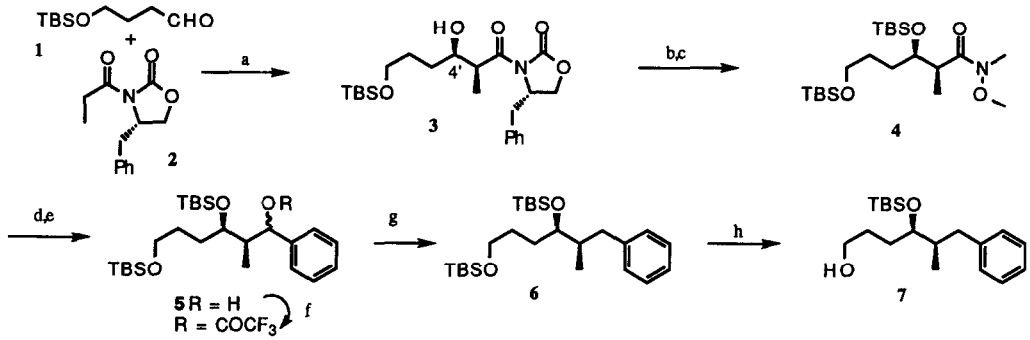


Zaragozic Acid C
L-697,350

The assembly of the C-1 sidechain of the less functionalized zaragozic acid C was initially examined. A straightforward approach utilizing chiral oxazolidinone aldol chemistry[3] for installing the two chiral centers was undertaken (Scheme I). Treatment of the readily available 1,4-butanal ether **1**[4] with the boron enolate of the chiral (S)-oxazolidinone **2** afforded good yields of the aldol adduct **3**, with >98% d.e. Various attempts at reductive removal of the chiral auxiliary of **3** gave poor yields as well as partial deprotection of the silyl ethers. Along alternate lines, formation of the Weinreb amide[5] followed by protection of the β-hydroxyl moiety afforded the doubly protected diol **4** in 87% overall yield from **3**. Reduction of the Weinreb amide **4** with Dibal-H at -78°C followed by treatment of the resultant aldehyde with phenylmagnesium bromide yielded intermediate **5** in 85%. Several attempts at benzylic deoxygenation of the carbinol **5** were sluggish and low yielding. However formation of the trifluoroacetate derivative followed by mild reductive conditions (10% Pd/C, H_2, 15 psi, EtOAc, r.t.) afforded the deoxygenated bis-ether **6** in 91% overall yield. Selective removal of the primary silyl group was effected in quantitative yield by treatment of **6** with HF/pyridine in THF[6] to afford alcohol **7** $[\alpha]^{24}$ +12.8° (*c* 2.2, $CHCl_3$), thus completing the synthesis of the sidechain of zaragozic acid C. The high overall yields and simple experimental procedures allowed the rapid preparation of 82 grams of alcohol **7** in a single run. The availability of

this alcohol has allowed facile preparation of the corresponding bromide, acid, aldehyde, and several other derivatives.

Scheme 1



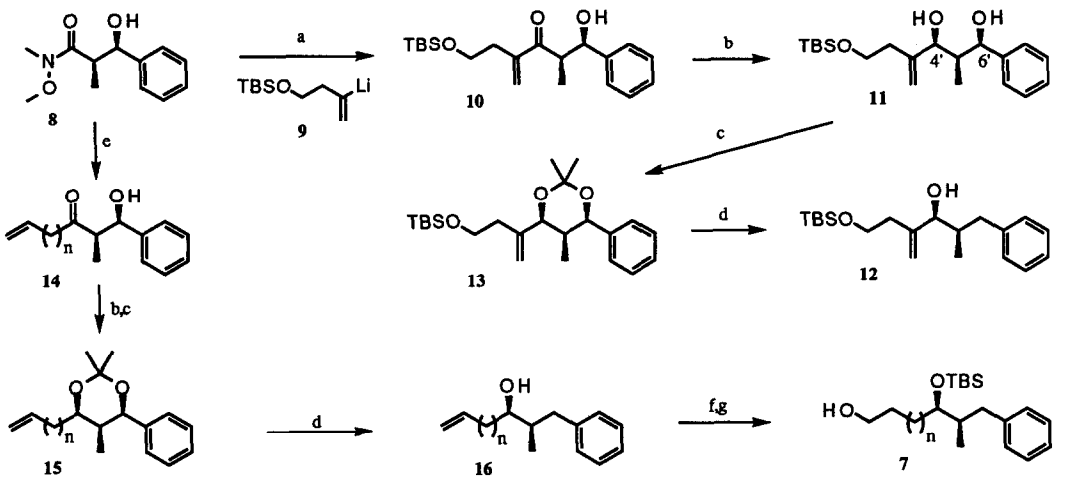
Reagents: a) Bu_2BOTf, Et_3N, H_2O_2, CH_2Cl_2, 70%; b) Me_3Al, MeNHOMe, CH_2Cl_2, 0°C, 91%; c) TBSOTf, Et_3N, CH_2Cl_2, -78°C, 96%; d) Dibal-H, THF, -78°C, 98%; e) PhMgBr, Et_2O, 0°C, 88%; f) TFAA, pyr., CH_2Cl_2, 0°C, 97%; g) H_2, 10% Pd/C, EtOAc, 90%; h) HF-pyr., THF, pyr., 98%.

With the synthesis of the simpler zaragozic acid C sidechain completed, utilization of this approach towards the synthesis of the zaragozic acid A sidechain was examined. Initial attempts at installation of the C-3' α-methylene into the corresponding aldehyde **1** prior to the aldol condensation were unyielding. More successfully, an alternative approach (Scheme II) involved reaction of the known Weinreb amide **8**[7] with the TBS ether of 3-lithio-3-butenol **9** (prepared from reaction of the 3-bromo derivative[8] with *tert*-butyllithium)[9] to afford enone **10** in 68% yield (58% overall yield from benzaldehyde). Chelate controlled reduction of the enone **10** was accomplished *via* the Sandoz procedure[10] with >98:2 selectivity and 85% purified yield of diol **11**. Selective benzylic deoxygenation of **11** was complicated by competitive reaction of the allylic hydroxyl moiety. Numerous attempts at deoxygenation resulted in reduction of the olefin and/or hydrogenolysis of the allylic hydroxyl group. Best results were obtained by treatment of **11** with excess Li° in liquid NH_3 at -40°C for >5 h and gave the desired deoxygenated derivative **12** in a modest 40% yield. A marked improvement to this transformation was effected by preparation of the acetonide **13** followed by Li°/NH_3 reduction which afforded in quantitative yield the desired alcohol **12** with complete chemoselectivity.

This alternate approach utilized a stereodefined C-6' benzylic hydroxyl to induce the asymmetry at the prochiral C-4' position (**10**→**11**). Note that the previous approach (Scheme 1) set the C-4' stereocenter *via* a chiral aldol of the opposite sense (**2**→**3**). The ability to alter the nature of the nucleophile (i.e. **9**) to allow for preparation of several different derivatives later in the synthesis and the brevity of this approach were two distinct advantages of this latter route. Assembly of the zaragozic acid C sidechain from addition of the corresponding allyl nucleophile was thus straightforward.

Treatment of amide **8** with allylmagnesium bromide, to afford ketone **14**, followed by chelate-controlled reduction and acetonide formation produced **15** in 83% overall yield. Selective deoxygenation gave a near quantitative yield of the alkenol **16** (n=1). Protection of **16** as the silyl ether followed by hydroboration-oxidation afforded the alcohol **7** (n=1),[11] $[\alpha]^{24}$ +12.2° (*c* 2.15, $CHCl_3$), in excellent yield. To further illustrate the versatility of this approach for derivitization, this protocol was utilized to prepare the corresponding n=2-7 sidechain analogs in comparable yield from the corresponding alkenyl Grignard (RBr, Mg°, THF, r.t.) and either olefin hydration or reductive ozonolysis to afford the requisite alcohols **7** (n=2-7).

Scheme II



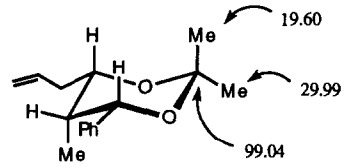
Reagents: a) RLi, THF, -78°C, 68%(91%); b) Et_2BOMe, $NaBH_4$, HOAc, H_2O_2, MeOH, 85%; c) $(MeO)_2C(Me)_2$, PPTS, PhH, 98%; d) Li^o NH_3, THF, -60°C, 100%; e) allylMgBr, THF, 0°C, 93%; f) TBSOTf, Et_3N, CH_2Cl_2, -78°C, 98%; g) 9-BBN, THF, 3M NaOH, H_2O_2, 98%.

Stereochemical assignment of the C-4' hydroxyl (presumably set by chelation controlled reduction) was reinforced by examination of the ^{13}C NMR data of the corresponding acetonide **15**. Chemical shift correlation of the ^{13}C NMR resonances of the three acetonide carbons has been shown to be a reliable method for determination of the relative stereochemistry of acyclic 1,3 diols.[12] The data obtained for acetonide **15** indicate the desired syn relationship between the hydroxyls (Scheme 3). In addition, nonselective reduction ($NaBH_4$, MeOH, r.t.) of β-hydroxy ketone **14** (n=1) afforded some of the presumed anti diol which showed corresponding acetonide ^{13}C NMR resonances in agreement with the anti relationship.

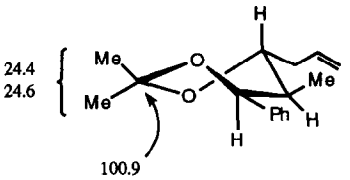
Scheme III ^{13}C **NMR Data (ppm)**

Syn Polyols[12] (ave ± σ): 19.4 ± 0.21, 30.0 ± 0.15, 98.1 ± 0.83

Trans Polyols[12] (ave ± σ): 24.6 ± 0.76, 24.6 ± 0.76, 100.6 ± 0.25



SYN-15



ANTI-15

The utility of the routes to the sidechains of the zaragozic acids has been demonstrated by the efficient preparation of multigram quantities of the zaragozic acid C C-1 sidechain. In addition, the alternate approach allowed for the easy assembly of various chainlength and functionalized derivatives.

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