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A General Access to Zaragozic Acids: Total Synthesis and Structure Elucidation of Zaragozic Acid D and Formal Syntheses of Zaragozic Acids A and C

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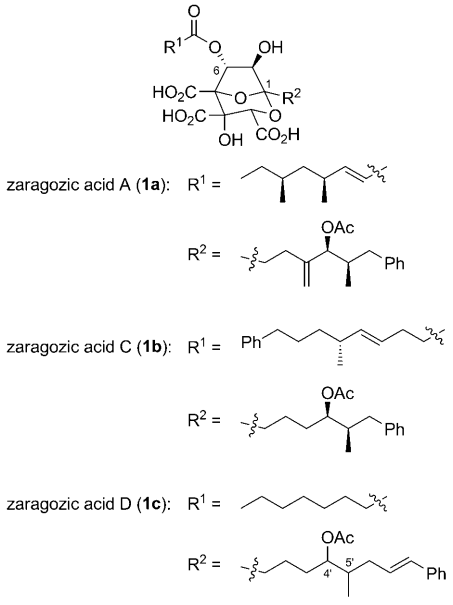
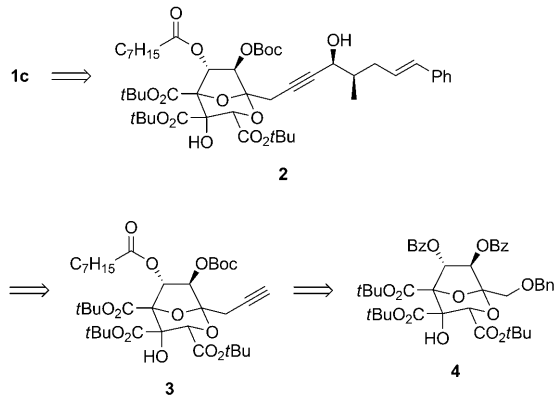
The zaragozic acids or squalestatins have been isolated from various fungi. They are nano- to picomolar inhibitors of the squalene synthase of mammals and fungi and therefore, inhibit very efficiently the biosynthesis of cholesterol and show fungicidal properties. A few examples also inhibit *ras*-farnesyl protein transferase at nanomolar concentrations, which might be interesting for the development of antitumor agents.[1] In more recent studies it was shown that these compounds can also cure prion-infected neurons and protect against prion neurotoxicity,[2] as well as sensitize acute myeloid leukemia cells (AML) to radiochemotherapy.[3] Almost all zaragozic acids share a highly oxygenated heterobicyclic core, whereas structural differences reside in the alkyl side chain at C1 and the ester side chain at C6. Due to their strong physiological effects and complex molecular structure, these natural products have stimulated enormous synthetic efforts, some of which have already culminated in several total syntheses of zaragozic acid A (**1a**)[4] and zaragozic acid C (**1b**),[4f,5] as well as the less oxygenated representative 6,7-dideoxysqualestatin H5.[6] We recently communicated an efficient symmetry-based route to the 2,8-dioxabicyclo-[3.2.1]octane derivative **4**, which offers itself as a general building block for zaragozic acids by virtue of its functionality.[7] Herein, we present the application of **4** to the first total synthesis of zaragozic acid D (**1c**), which has also enabled the assignment of its hitherto unknown configuration at C4′ and C5′. In addition, we describe the utilization of **4** for a formal synthesis of **1a** and **1b**.



Zaragozic acid D (**1c**) is one of the most active *ras*-farnesyl protein transferase inhibitors in this natural product series with an IC_{50} of 100 nM.[8,9] A comparison with the structures of **1a** and **1b** suggested that the *syn* configuration in the alkyl side chain of these acids was most likely for **1c** as well. Retrosynthetically, compound **1c** was traced back to propargylic alcohol **2**, which in turn could be prepared from terminal alkyne **3**, which should be available from the heterobicyclic compound **4** (Scheme 1).



Scheme 1. Retrosynthetic analysis for zaragozic acid D (**1c**).

Following debenzylation of **4** and subsequent Swern oxidation of primary alcohol **5**, a cerium acetylide could be attached chemoselectively[10] to the resulting aldehyde to give a diastereomeric mixture of propargylic alcohol **6** (Scheme 2). Transformation of **6** to thionocarbonates **7** set

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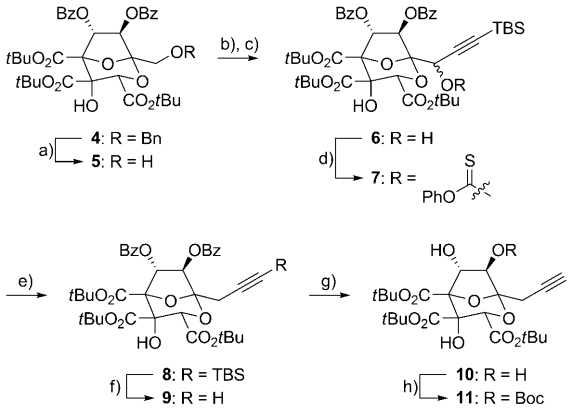
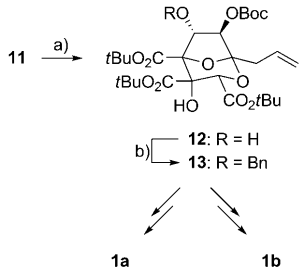


Scheme 2. Conversion of the heterobicyclic building block **4** to alkyne **11**. a) H_2, 10% Pd/C, HOAc (1 equiv), EtOAc, RT, 98%; b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C→−10°C; c) Cl_2Ce–C≡C–TBS, THF, −78°C, 87% (2 steps); d) Cl(PhO)C=S, DMAP, CH_2Cl_2, 0°C→RT, 97%; e) Bu_3SnH, AIBN, benzene, reflux, 95%; f) Bu_4NF, HOAc, THF, 0°C→RT, 98%; g) K_2CO_3, MeOH, 16°C, 73% **10** (+17% monomethyl ester); h) $(Boc)_2O$, Et_3N, 4-pyrrolidinopyridine, CH_2Cl_2, −3°C, 89%. Bn=benzyl, Bz=benzoyl, TBS=*tert*-butyldimethylsilyl, DMAP=4-(*N*,*N*-dimethylamino)pyridine, AIBN=azobisisobutyronitrile, Boc=*tert*-butoxycarbonyl.

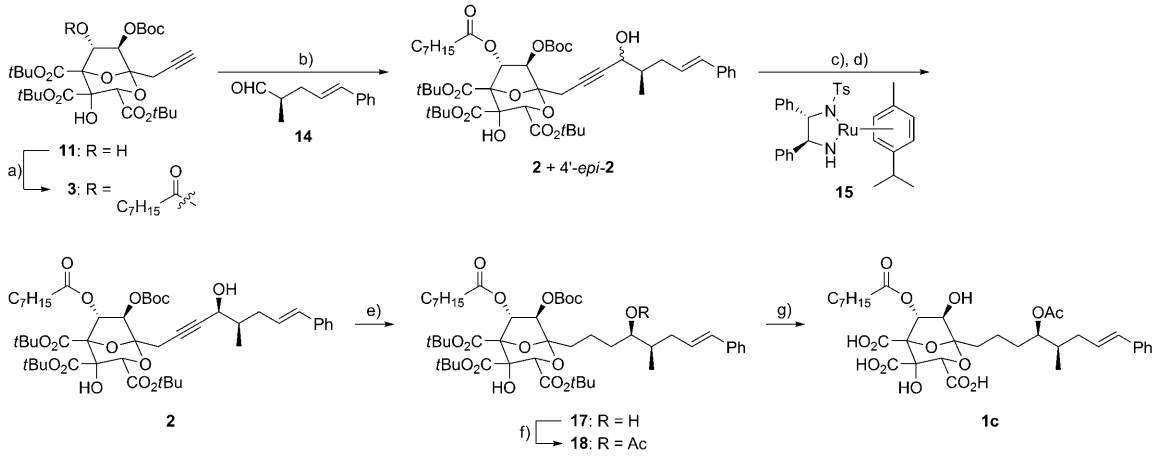


Scheme 3. Formal synthesis of **1a** and **1b** via alkene **13**. a) H_2, Lindlar catalyst, quinoline, benzene, RT, 100%; b) BnBr, Ag_2O, toluene, RT→40°C, 62% (98% based on recovered starting material (borsm)).

the stage for a smooth radical deoxygenation with tributyltin hydride[11] to afford **8**. Sequential removal of the *tert*-butyldimethylsilyl (TBS) unit to give **9** and cleavage of both benzoyl protecting groups by transesterification gave the desired triol **10** and a small amount of a corresponding monomethyl ester. As anticipated,[5b] a highly selective protection of the C7 hydroxyl group of the tri-*tert*-butyl ester **10** gave the Boc derivative **11**.

At this stage we accomplished a formal synthesis of **1a** and **1b** through transformation of alkyne diol **11** to alkene **13**, which had already been converted to the two natural products **1a** and **1b** by Hashimoto (Scheme 3).[4f] Lindlar semi-hydrogenation of **11** proceeded smoothly, and after chemoselective benzylation of the secondary alcohol of the resulting diol **12**, the advanced intermediate **13** was isolated which was identical to the reference compound in all respects.[12]

For the synthesis of **1c**, the secondary alcohol of **11** was esterified with octanoyl chloride to give intermediate **3** (Scheme 4). Addition of this polyfunctional alkyne **3** to the known aldehyde **14**,[13] without partial racemization of the latter, was accomplished via the zinc derivative of **3**, which was generated under mild conditions with diethylzinc in the presence of (−)-*N*-methylephedrine.[14] The diastereomeric mixture of **2** and 4′-*epi*-**2** (1:2) obtained in this way was unified by Dess–Martin periodinane oxidation followed by an asymmetric transfer hydrogenation of the resultant alkynone with the ruthenium catalyst **15** and isopropanol as the hydride source[15] to afford **2** with excellent stereoselectivity (diastereomeric ratio (d.r.) ≥ 20:1). The challenging chemoselective complete alkyne reduction of the propargyl alcohol moiety in the presence of the styrene unit (as part of a bishomoallylic alcohol) was cleanly achieved by a hydroxyl-directed hydrogenation of **2** with ruthenium catalyst **16**.[16,17]



Scheme 4. Completion of the synthesis of **1c**. a) C_7H_{15}–COCl, DMAP, CH_2Cl_2, 0°C→RT, 97%; b) i) Et_2Zn, (−)-*N*-methylephedrine (15 mol%), toluene, 0°C, ii) **14**, 0°C→RT, 51% (85% borsm); c) Dess–Martin periodinane, CH_2Cl_2, RT; d) **15** (5 mol%), *i*PrOH, RT, 86% (2 steps); e) 55 bar H_2, [Ru{(*S*)-binap}$(OAc)_2$] (**16**, 2 mol%), MeOH, RT, 75% **17** (+24% diene); f) Ac_2O, DMAP, CH_2Cl_2, 0°C, 99%; g) TFA, CH_2Cl_2, reflux, 100%. binap=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, TFA=trifluoroacetic acid.

After acetylation of the hydrogenation product **17** to give **18**, the three *tert*-butyl esters, as well as the Boc protecting group on the C7 hydroxyl group, were readily removed by TFA to give **1c**, which was isolated as a white solid and identical to the natural product in all respects.[18]

In summary, the heterobicyclic building block **4** was elaborated to zaragozic acid D (**1c**) in an efficient fashion, which also established the configuration of this natural product at the C4′- and C5′-positions. Since compound **4** allowed a formal synthesis of zaragozic acids A (**1a**) and C (**1b**) as well via the Hashimoto intermediate **13**, it can indeed be regarded as a general advanced precursor for members of this group of bioactive natural products and non-natural analogues.

Acknowledgements

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Keywords: alkynylation · asymmetric catalysis · chemoselectivity · natural products · total synthesis

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[12] Compound **13** prepared from **11**: $[\alpha]_D^{25} = -11.2$ ($c = 1.38$, $CHCl_3$); see Ref. [4f]: $[\alpha]_D^{25} = -10.9$ ($c = 1.32$, $CHCl_3$).

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[17] Next to allyl alcohols, homoallyl alcohols are also hydrogenated with catalyst **16**, whereas a bishomoallyl alcohol was reported to be inert under comparable hydrogenation conditions (see Ref. [16]). Interestingly, propargyl alcohol **2** could be selectively hydrogenated with **16** to give the corresponding allyl alcohol under carefully controlled conditions.

[18] Synthetic **1c**: $[\alpha]_D^{22} = +16.7$ ($c = 1.38$, MeOH); natural **1c** (see Ref. [8]): $[\alpha]_D^{25} = +13.7$ ($c = 1.8$, MeOH).

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