Natural Product Synthesis

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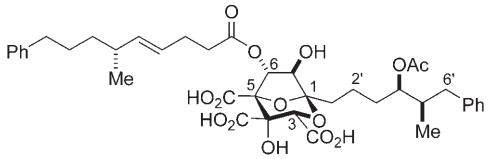
Formal Total Synthesis of (+)-Zaragozic Acid C through an Ireland–Claisen Rearrangement**

*Jens O. Bunte, Anthony N. Cuzzupe, Alica M. Daly, and Mark A. Rizzacasa**

The zaragozic acids[1] and squalestatins[2] are structurally related fungal metabolites isolated independently by several industrial research groups in the early 1990s.[3] These compounds were identified as potent inhibitors[4] of squalene synthase and showed promise as cholesterol-lowering compounds.[5] In addition, some zaragozic acids inhibit farnesyl protein transferase and thus show potential as antitumor agents.[6] The engrossing, highly oxygenated 2,8-dioxabicyclo-[3.2.1]octane core present in these compounds coupled with their biological activity sparked great interest within the synthetic community which, to date, has culminated in five total syntheses[7] of zaragozic acid C (**1**),[8] three syntheses of its congener zaragozic acid A,[9] and one synthesis of the related 6,7-dideoxysqualestatin H5.[10] Herein, we report a synthesis of an advanced intermediate which has been converted into **1**.



1: Zaragozic acid C

Our retrosynthetic analysis of **1** is shown in Scheme 1. The primary target was known intermediate **2**, which was converted into zaragozic acid C (**1**) in four steps.[8a] It was envisaged that triacetate **2** could be formed by methanolysis[10] of the spirolactone acetal **3** and subsequent acid-mediated cyclization to secure the 2,8-dioxabicyclo-[3.2.1]octane core. Functional-group manipulations would

[*] Dr. J. O. Bunte, Dr. A. N. Cuzzupe, A. M. Daly, Prof. Dr. M. A. Rizzacasa
School of Chemistry
The University of Melbourne
Bio21 Institute, 30 Flemmington Road
Melbourne, Victoria 3010 (Australia)
Fax: (+61) 3-9347-8396
E-mail: masr@unimelb.edu.au
Homepage: http://www.chemistry.unimelb.edu.au/staff/masr/research/MARHomepage.html

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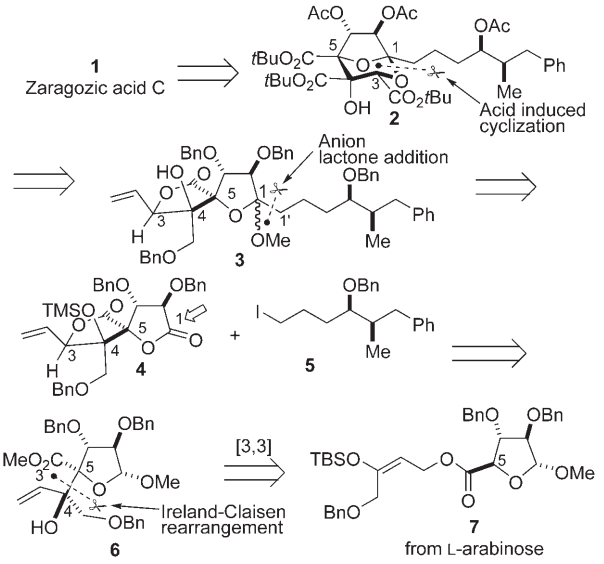
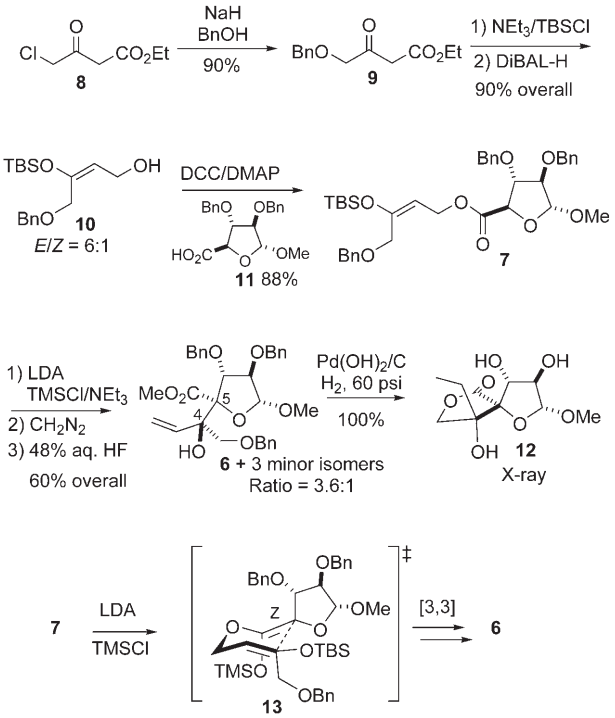


Scheme 1. Retrosynthetic analysis of zaragozic acid C (**1**). Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



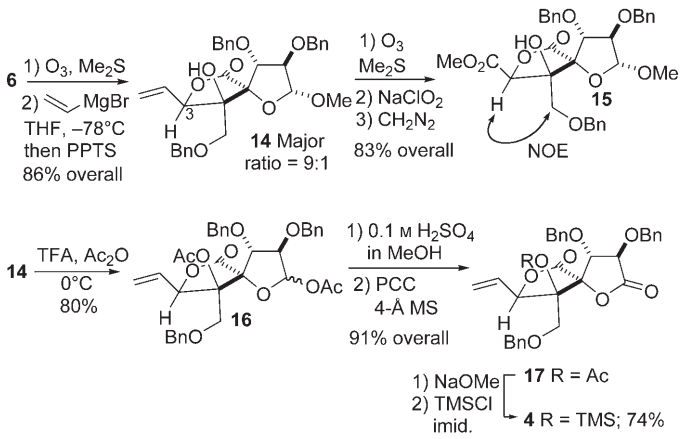
Scheme 2. Synthesis of ester **6**. DCC = dicyclohexylcarbodiimide, DiBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, LDA = lithium diisopropylamide.

then give the triacetate **2**. The acetal **3** could be formed by regioselective addition[11] of the lithium anion derived from the side-chain iodide **5** to the less-hindered C1 carbonyl group[12] of the spirobislactone **4**. Compound **4** could be obtained from tertiary alcohol **6**, which in turn would be formed by an Ireland–Claisen rearrangement in the presence of a β leaving group[13] of the sensitive allylic ester **7** derived from L-arabinose. This key transformation would form the C4–C5 bond and the two quaternary asymmetric centers simultaneously.[14] Furthermore, intermediate **6** contains all the asymmetric centers required for the core system apart from that at C3. We have previously utilized the Ireland–Claisen rearrangement of allyl furanosiduronates in the presence of a β leaving group for the synthesis of related 2-alkylcitrate natural products, such as cinatrins B,[15] C_1, and C_3,[16] as well as trachyspic acid[17] and a model zaragozic acid A system devoid of substituents at C4.[18]

The synthesis of the key intermediate **6** is outlined in Scheme 2. Treatment of ethyl 4-chloroacetoacetate (**8**) with the anion derived from benzyl alcohol afforded ether **9**.[19] Exposure of **9** to TBSCl and NEt_3[20] in THF at 50 °C followed by reduction with DiBAl-H gave the alcohol **10** as a 6:1 mixture of geometric isomers. DCC-mediated coupling of this alcohol with the L-arabinose derived acid **11**[21] afforded the Ireland–Claisen precursor **7**, which could be purified by rapid chromatography on silica gel. Treatment of a solution of the ester **7** in THF/hexamethylphosphoramide (HMPA) and the centrifugate from a 1:1 (v/v) mixture of TMSCl and NEt_3 with LDA at −100 °C[13b,c] gave the silyl ketene acetal, which underwent stereoselective [3,3] rearrangement upon warming to room temperature. Hydrolysis of the crude TMS ester followed by methylation and removal of the TBS group provided ester **6** as the major product along with three other minor diastereoisomers in 60% yield for the three steps and a ratio of 3.6:1, respectively. The desired ester **6** was readily separated from the other minor isomers by flash chromatography. One minor isomer (stereochemistry undetermined) was obtained pure, whereas the other two were isolated as a 63:37 mixture. The stereochemistry of **6** was determined by its conversion into the crystalline spirolactone **12** (Scheme 2). A single-crystal X-ray structure[22] was obtained for **12**, which confirmed the stereochemistry of the major product **6** of the Ireland–Claisen rearrangement. Interestingly, attempted rearrangement of the ester synthesized from the *para*-methoxybenzyl (PMB)-protected analogue of allyl alcohol **10** and acid **11** failed completely.

The outcome of the [3,3] rearrangement can be explained by considering the chairlike transition state **13** in which it is assumed that the geometry of the major ketene acetal formed is *Z*[23] (Scheme 2). The C5 stereochemistry results from rearrangement from the face opposite the β-benzyloxy group, whereas the C4 stereochemistry arises from the chairlike transition state as shown.

The conversion of the Claisen product **6** into the spirobislactone core precursor **4** is outlined in Scheme 3. We initially investigated the dihydroxylation of the alkene functionality in **6** as a means of introducing the C3 stereochemistry. Unfortunately, both simple catalytic[24] or asymmetric[25] dihydroxylation of **6** resulted in preferential formation of the isomer with undesired stereochemistry at C3. This result led to an alternative method for the introduction of the C3 stereochemistry. Ozonolysis of the alkene **6** provided an aldehyde and chelation-controlled addition[9e] of vinylmagnesium bromide and gave the desired lactone **14** in a stereoselective manner (90% d.r.) after acid treatment to complete lactonization. The stereochemistry for spirolactone

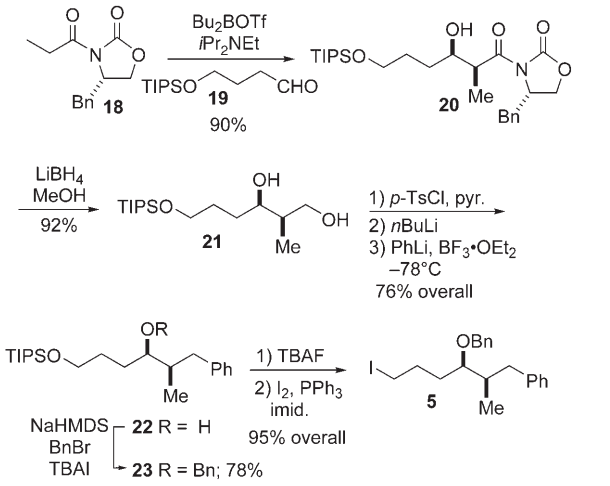


Scheme 3. Synthesis of spirobislactone **4**. imid. = imidazole, MS = molecular sieves, PCC = pyridinium chlorochromate, PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid.

14 was assigned based on NOE interactions observed between H3 and the C4 methylene group in the derived C3 methyl ester **15**.

The hydrolysis of the methyl ketal in **14** proved troublesome as most acidic methods caused extensive decomposition of the substrate. Eventually, we found that acetolysis (Ac_2O, TFA, 0 °C)[26] cleanly gave the diacetate **16** as a 2:1 mixture of anomers. Higher temperatures also resulted in acetolysis of the benzyl groups. The anomeric acetate could now be readily cleaved with dilute acid and oxidation gave the lactone **17**. Selective acetate methanolysis followed by TMS protection provided the spirobislactone core precursor **4** in good yield.

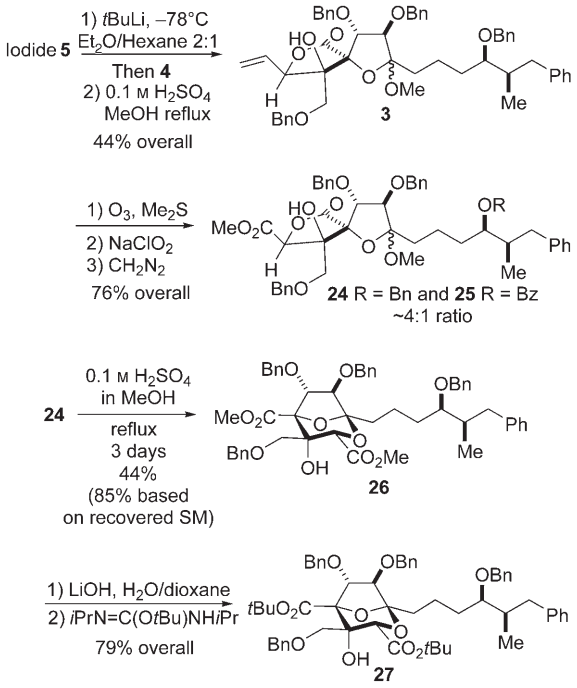
With the required spirobislactone **4** in hand, we then synthesized the iodide **5** required for the C1 side chain as outlined in Scheme 4. Thus, an Evans aldol reaction[27] between the boron enolate derived from oxazolidinone **18** and aldehyde **19**[28] proceeded in excellent yield and stereoselectivity (> 95 % *de*) to afford adduct **20**. Reductive



Scheme 4. Synthesis of the side-chain iodide **5**. OTf = triflate, pyr. = pyridine, NaHMDS = sodium hexamethyldisilazane, TBAI = tetrabutylammonium iodide, TBAF = tetrabutylammonium fluoride, TIPS = triisopropylsilyl, *p*-TsCl = *p*-toluenesulfonyl chloride.

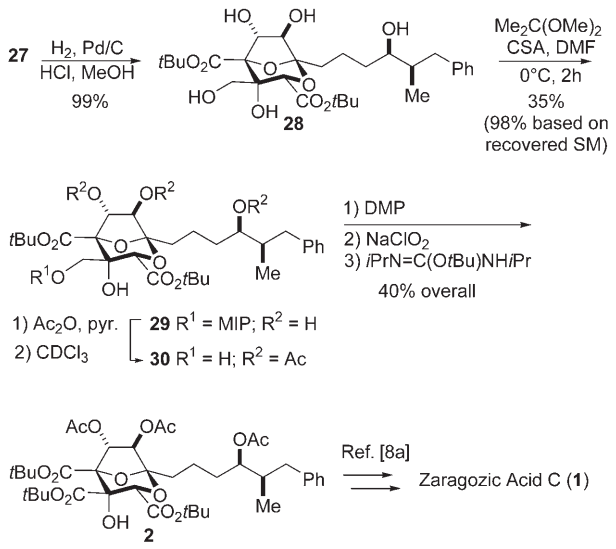
removal of the chiral auxiliary provided diol **21**, which was converted into the primary monotosylate and treatment of this with *n*BuLi resulted in oxetane formation.[8a] Ring opening of the oxetane with PhLi in the presence of a Lewis acid gave alcohol **22** in good overall yield. We found that the synthesis and isolation of the oxetane gave better yields than the one-pot process reported by Carreira and Du Bois.[8a] Benzyl group protection proceeded best with NaHMDS as the base to afford ether **23**, and fluoride-induced desilylation followed by conversion of the primary alcohol into the iodide[29] gave the side-chain fragment **5** in excellent yield.

The final steps to the zaragozic acid C intermediate **2** are outlined in Schemes 5 and 6. Treatment of **5** with *t*BuLi[30] in a Et_2O/hexane solvent mixture at −78 °C generated the lithium



Scheme 5. Synthesis of the 2,8-dioxabicyclo[3.2.1]octane **27**. SM = starting material, Bz = benzoyl.

anion, which selectively added to spirolactone **4** at the C1 carbonyl group (2.2:1 ratio of addition products; 72 % yield). Treatment of the C1 addition product with acidic methanol, however, gave the methyl ketals **3** as a separable mixture and only a trace (2 % yield) of the desired 2,8-dioxa-[3.2.1]bicyclooctane. We surmised that the slow step in the acid-catalyzed process may be opening of the lactone ring and therefore decided that a decrease in electron density would assist the methanolysis. Therefore, alkene **3** was oxidatively cleaved and oxidation[31] followed by methylation afforded methyl ester **24** along with a by-product **25**, as a result of oxidation of the side-chain O4′ benzyl protecting group.[32] To our delight, treatment of a mixture of ketals **24** with 0.1 M sulfuric acid in boiling methanol resulted in the formation of the desired zaragozic acid core system **26** in 44 % yield along with recovered methyl ketals **24** (85 % based on recovered



Scheme 6. Completion of the formal total synthesis of zaragozic acid C (**1**). CSA = 10-camphorsulfonic acid, DMP = Dess–Martin periodinane, DMF = *N*,*N*-dimethylformamide, MIP = methoxyisopropyl.

24). Hydrolysis of the methyl esters and formation[33] of the di-*tert*-butyl ester gave bicycle **27**.

The final major synthetic challenge was the selective functionalization of the C4 primary alcohol. This quest began with global debenzylation through hydrogenolysis to give pentol **28** in high yield.[34] Numerous experiments to selectively protect the C4 primary alcohol failed. In one case, to form the dimethylacetonide of the 1,2-diol at C4, pentol **28** was exposed to 2,2-dimethoxypropane in DMF in the presence of catalytic CSA, which resulted in the formation of an undesired acetonide between the primary alcohol and the C7 hydroxy group. However, during the course of monitoring this reaction by TLC, we initially noticed the selective formation of a spot at a higher R_f value which slowly disappeared and a spot at a lower R_f value, which corresponds to the undesired acetonide, was formed. Treatment of **28** with the same reagents as above, but at 0 °C for a shorter time, selectively afforded the compound with a higher R_f value, which was identified as methoxyisopropyl (MIP) ether **29**, along with recovered starting material **28**, which could readily be recycled. This serendipitous discovery led to the monoprotection of pentol **28** with a highly acid-labile protecting group. Acetylation of **29** and treatment with mild acid[35] gave alcohol **30**, which upon two-stage oxidation and ester formation yielded the target compound **2**, the physical data for which were identical to those reported.[8a,c]

In conclusion, we have completed a synthesis the precursor of zaragozic acid C (**1**), in which the C4–C5 bond was formed in a stereoselective manner with concomitant formation of the quaternary asymmetric centers by an Ireland–Claisen rearrangement of the sensitive allylic ester **7**. Other highlights of this route include a novel acetolysis of the methyl ketal **15**, selective carbanion addition to the spirobislactone **4**, methanolysis of lactone **24**, subsequent formation of the zaragozic acid bicycle **26**, and a selective MIP group protection of pentol **28**. Studies towards the synthesis of other members of the zarazozic acid/squalestatin family are underway.

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