Review

Total Synthesis of the Squalene Synthase Inhibitor Zaragozic Acid C

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Zaragozic acids and squalestatins were documented by Merck, Glaxo, and Tokyo Noko University/Mitsubishi Kasei Corporation as part of a program aimed at identifying novel inhibitors of squalene synthase, as well as farnesyl transferase. These natural products have attracted considerable attention from numerous synthetic chemists because of their therapeutic potential and novel architecture. This review highlights our total syntheses of zaragozic acid C by two convergent strategies. The key steps in our first-generation synthesis involve 1) simultaneous creation of the C4 and C5 quaternary stereocenters through the $Sn(OTf)_2$-promoted aldol coupling reaction between the α-keto ester and silyl ketene thioacetal derived from L- and D-tartaric acids, respectively; and 2) construction of the bicyclic core structure *via* acid-catalyzed internal ketalization under kinetically controlled conditions. The second-generation strategy relies on a tandem carbonyl ylide formation/1,3-dipolar cycloaddition approach and features elongation of the C1 alkyl side chain through an olefin cross-metathesis as well as high convergency and flexibility.

Key words zaragozic acid; total synthesis; carbonyl ylide cycloaddition; olefin cross-metathesis; internal ketalization; aldol reaction

1. Introduction

Natural products have played a significant role in the development of organic chemistry, especially in the area of fine organic synthesis. Compounds with unprecedented molecular architecture and multiple functional groups have created opportunities for devising new strategies and methodologies as well as evaluating the practicability of known methods and reactions. In addition, making target molecules in a practical fashion represents one of the major challenges in synthetic organic chemistry.

A cascade sequence can lead to an increase in molecular complexity by combining a series of reactions in one synthetic operation. Designing a "one-pot" sequence for the construction of highly complex molecules might provide one good solution to the foregoing problem, *i.e.*, practical synthesis. In this context, we have explored the tandem carbonyl ylide formation/1,3-dipolar cycloaddition methodology for the construction of the common 2,8-dioxabicyclo[3.2.1]octane structure of zaragozic acids,[1,2] while the viability of the dispiroketalization *via* a tandem double hemiketal formation/intramolecular hetero-Michael addition process was investigated during the course of our synthetic studies on the shellfish poison pinnatoxin A.[3—5] As space is limited, this review highlights our total syntheses of zaragozic acid C using two convergent approaches, the comparison of which might confirm the power and vitality of the tandem reaction sequence in the synthesis of natural products.

2. Zaragozic Acids

The zaragozic acids[6—11] and squalestatins,[12—15] fungal metabolites isolated and characterized independently by researchers at Merck, Glaxo, and Tokyo Noko University/Mitsubishi Kasei Corporation in 1992, have been shown to be picomolar competitive inhibitors of the enzyme squalene synthase (Fig. 1). Consequently, they are regarded as promising lead compounds for the development of new serum cholesterol-lowering drugs.[16—18] Some members of this family have also been found to display *ras* farnesyl-protein transferase inhibitory activity,[8,19] which has implications in the development of anticancer chemotherapeutics.

Structurally, these molecules share a 4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core with an array of six stereogenic centers including contiguous quaternary ones and show considerable variations in the C1 alkyl

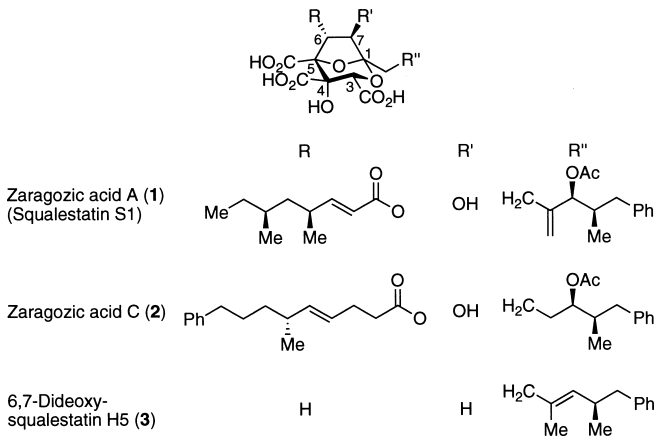

Fig. 1. Structure of Representative Members of the Zaragozic Acid Family

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and C6 acyl side chains. It is therefore not surprising that the zaragozic acids (squalestatins) have elicited considerable attention from numerous synthetic chemists. Over 30 groups have made impressive contributions to the literature on the synthesis of these molecules.[20—23] Of a variety of approaches to the densely oxygenated 2,8-dioxabicyclo-[3.2.1]octane ring system by devising innovative strategies and tactics, the two research groups of Carreira[24,25] and Nicolaou[26—29] accomplished the first total syntheses of zaragozic acid C and zaragozic acid A, respectively, in 1994. Since then the Evans[30] and Armstrong[31,32] groups have accomplished the total syntheses of zaragozic acid C, while the efforts of the groups of Heathcock,[33,34] and Tomooka and Nakai[35] culminated in successful total syntheses of zaragozic acid A. These approaches are summarized in Chart 1. All of these approaches involve internal ketalization to construct the core structure; only Heathcock and co-workers adopted a stepwise approach, wherein the full C1 alkyl side chain was installed after the ketalization event. The focal point of the Carreira strategy is the use of O4 benzyl-pro-

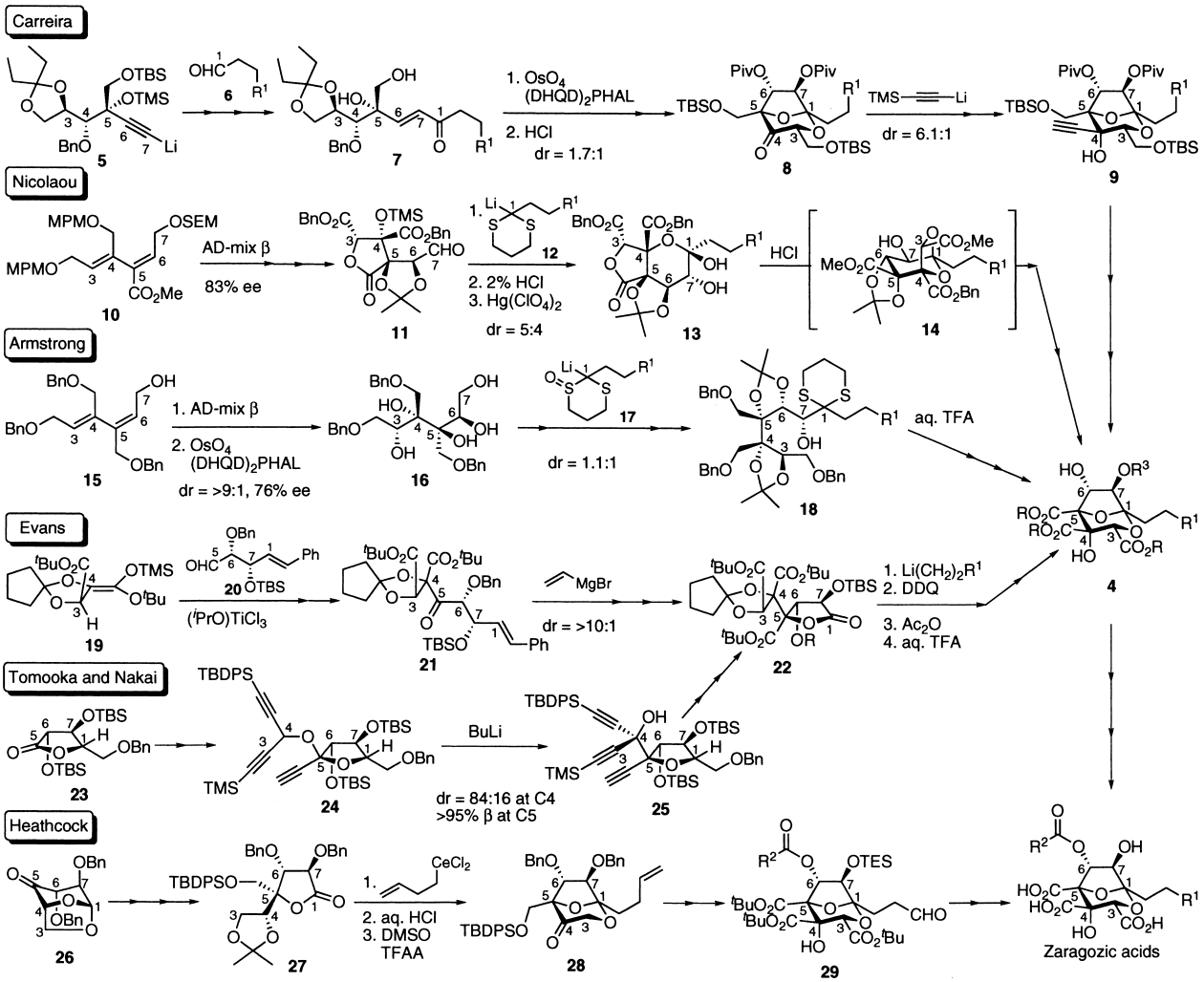


Chart 1. Total Syntheses of Zaragozic Acids A and C by Other Groups

Seiichi Nakamura was born in Tokyo on 2 January 1967. He received his bachelor's degree from the University of Tokyo in 1989 while conducting research under the direction of Professor Masaji Ohno. He obtained his Ph. D. degree from the University of Tokyo in 1994 working on the synthesis of a protein phosphatase inhibitor tautomycin under the supervision of Professor Masakatsu Shibasaki. From 1993 to 1994, he worked as a Research Fellow of the Japan Society for the Promotion of Science. In 1994, he joined the research group of Professor Shunichi Hashimoto at Hokkaido University as Instructor, and was promoted to Associate Professor in 2004. That same year he received the Pharmaceutical Society of Japan Award for Young Scientists.

Seiichi Nakamura

tected tetrahydroxyketone, prepared by the coupling of lithium acetylide **5** with aldehyde **6**, followed by the four-step sequence including dihydroxylation, as a ketalization precursor to avoid the concomitant formation of the isomeric bicyclic ketal. The quaternary stereocenter at C4 was created by the addition of lithium acetylide to ketone **8**. The Nicolaou synthesis commenced with regioselective, asymmetric dihydroxylation of diene **10**. The addition of lithiated dithiane **12** to aldehyde **11**, followed by deprotection of the C4 alcohol and dithioketal, set the stage for ketalization. Upon exposure to 1.8% HCl in MeOH at 78 °C, lactone **13** rearranged into the desired bicyclic ketal **4** *via* the undesired ketal isomer **14**. In a related study, Armstrong and co-workers independently reported a similar approach, wherein two-stage, double asymmetric dihydroxylation of **15** was used to give pentaol **16** in 45% yield and 76% ee. The Evans strategy entailed coupling the D-tartrate-derived silyl ketene acetal **19** with aldehyde **20**. Lewis acid-catalyzed reaction proceeded in a stereoselective manner to establish the quaternary stereocenter at C4, while the addition of vinylmagnesium bromide to ketone **21** created the stereocenter at C5. Installation of the C1 alkyl side chain was followed by exposure to aqueous TFA to yield the desired bicycloketal **4** as a single isomer. Tomooka and Nakai and co-workers presented their approach to zaragozic acid A (**1**) which involves a [1,2]-Wittig rearrangement of *O*-glycoside **24**, prepared from lactone **23** in two steps. Treatment of **24** with BuLi effected the rearrangement to **25**, establishing the stereocenters at C4 and C5 simultaneously. Alcohol **25** was successfully transformed to lactone **22** (R=TBS), conversion of which to **1** was uneventfully achieved following the strategy developed by Evans. The Heathcock synthesis commenced with anhydrosugar **26**, easily prepared from D-glucose. Attachment of the C1 alkyl side chain to lactone **27** *via* the cerium reagent was followed by treatment with HCl and oxidation to provide ketone **28**. Elongation of aldehyde **29**, obtained from **28** in a 20-step sequence including installation of C3 and C4 esters and the C6 acyl side chain, completed the total synthesis of zaragozic acid A (**1**) using a relay approach.

In addition to the six total syntheses mentioned above, the total synthesis of 6,7-dideoxysqualestatin H5 (**3**), a less oxygenated congener of zaragozic acids, has also been recorded by Martin and co-workers.[36,37] Our own efforts in this area have led to two reported syntheses of zaragozic acid C (**2**) based on an aldol approach[38] and a carbonyl ylide cycloaddition approach.[1,2] In the following sections, the details of our total syntheses are reviewed.

3. The Aldol Approach to Zaragozic Acid C

The main problem in zaragozic acid synthesis is the construction of the highly oxygenated bicyclic core bearing an array of six stereogenic centers, including contiguous quaternary ones. Our first-generation retrosynthetic analysis of zaragozic acid C (**2**) hinged on the identification of L- and D-tartaric acids in the core structure (Chart 2). While some concern arose over the formation of the isomeric bicycloketal **33**, we expected that the natural 2,8-dioxabicyclo[3.2.1]octane core structure **30** would be thermodynamically more stable than **33**. We envisioned that the addition of the metalated C1 alkyl side chain equivalent **35** to aldehyde **34**, followed by oxidation, would provide the ketalization precursor **32**.

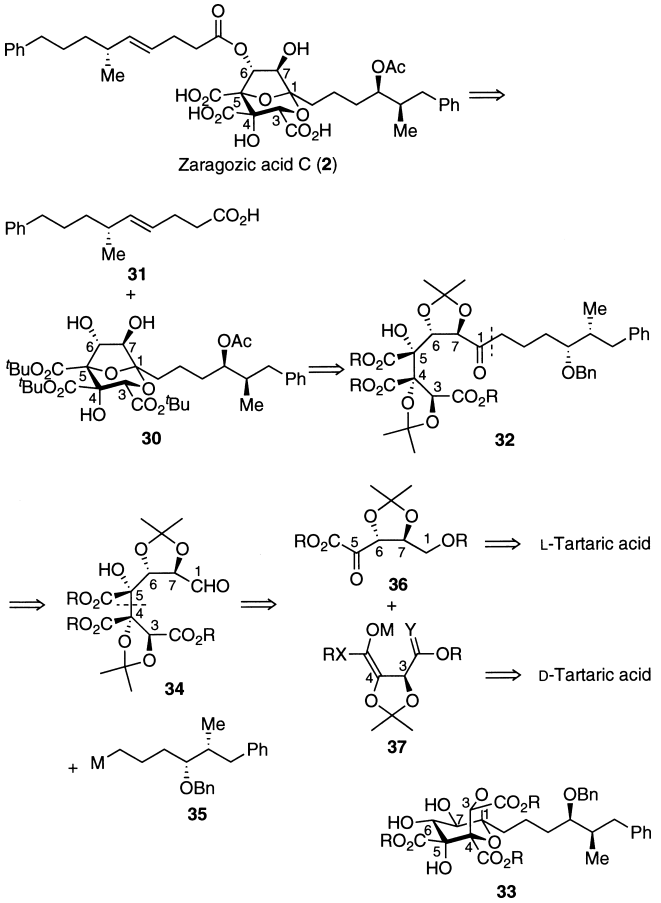


Chart 2. Retrosynthetic Analysis of Zaragozic Acid C (**2**) Based on an Aldol Strategy

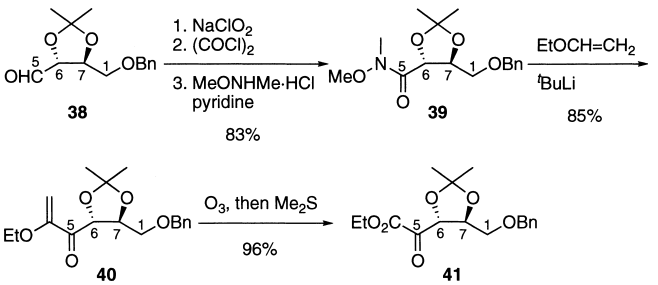


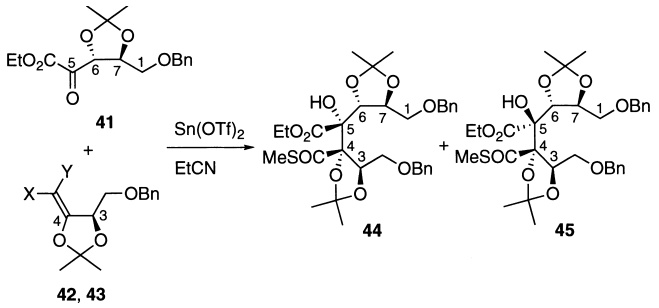
Chart 3. Preparation of α-Keto Ester **41**

The aldol moiety in **34** allowed the indicated disconnection, defining tartrate-derived α-keto ester **36** and enolate **37** as potential intermediates. This approach has the advantage of minimizing the use of protecting groups and oxidation state manipulations.

α-Keto ester **41** was prepared from the L-tartaric acid-derived aldehyde **38**[39] in five steps *via* the α-keto vinyl ether intermediate **40**[40] (Chart 3). Kraus oxidation[41] of **38** and treatment with $(COCl)_2$ were followed by condensation with *N*,*O*-dimethylhydroxylamine hydrochloride, affording the Weinreb amide **39**, which upon treatment with lithiated ethyl vinyl ether provided the α-keto vinyl ether **40**. Ozonolysis of **40** provided the desired α-keto ester **41** in 68% yield in five steps.

With the required α-keto ester **41** in hand, we then explored the aldol coupling between **41** and D-tartrate-derived

Table 1. $Sn(OTf)_2$-Promoted Aldol Coupling of Silyl Ketene Thioacetal **42** or **43** with α-Keto Ester **41**



	Silyl ketene		Temp. (°C)	Time (h)	Aldol adduct	
	X	Y			Yield (%)	**44** : **45**
42	SMe	OTMS	−70	1.5	90	1 : 2.2
43	OTMS	SMe	−55	1	36	1 : 10

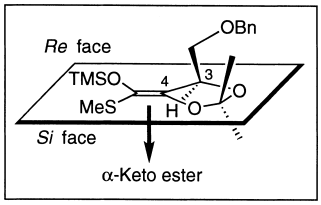


Fig. 2. Stereochemical Course of Aldol Reaction

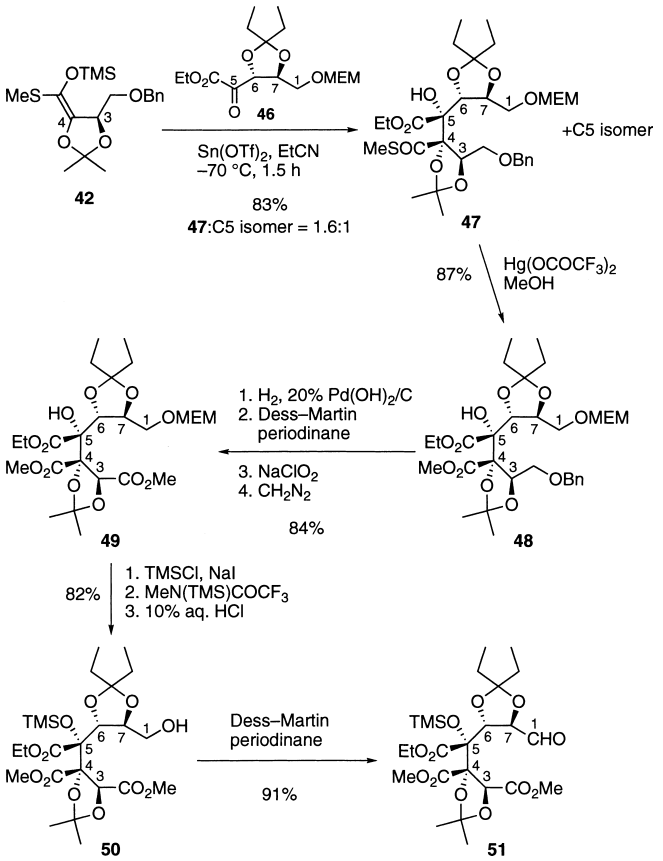


Chart 4. Synthesis of Aldehyde **51**

enolate. After considerable experimentation, it was found that aldol reaction of (*Z*)-silyl ketene thioacetal **42** with **41** under Kobayashi conditions [$Sn(OTf)_2$, EtCN, −70 °C][42] afforded a 1 : 2.2 mixture of adducts **44** and **45** of the four possible stereoisomers in a combined yield of 90% (Table 1). The stereochemistries of **44** and **45** were unambiguously established by ^1H NOE experiments on their derivatives. On the other hand, aldol reaction of (*E*)-silyl ketene thioacetal **43** with **41** did not occur at −70 °C but proceeded reluctantly at −55 °C to afford adducts in 36% yield with 1 : 10 stereoselectivity favoring the undesired diastereomer **45**. These results suggested that the *si* face of silyl ketene thioacetal **42** or **43** was more accessible to attacking α-keto ester **41** due to the steric demands of the benzyloxymethyl group, creating the proper configuration at C4 (Fig. 2); however, the preference for α-keto ester **41** to undergo *anti*-Felkin addition was observed, although the degree of carbonyl facial control was influenced by the geometry of the silyl ketene thioacetal. In an effort to reverse the stereochemical outcome of the aldol reaction to give the desired stereoisomer, a number of α-keto esters and silyl ketene thioacetals were synthesized and evaluated as substrates for the $Sn(OTf)_2$-promoted aldol reaction. The best combination of protecting groups for each reaction partner appeared to be for **42** and **46**,[43] respectively, affording a 1.6 : 1 mixture of aldol adducts favoring the desired isomer **47** (Chart 4).

Leaving this stereochemical problem aside, we then proceeded to the elaboration of the cyclization precursor. Methanolysis of the thioester was accomplished by treatment of **47** with $Hg(OCOCF_3)_2$ in MeOH, providing methyl ester **48** in 87% yield. Debenzylation was followed by oxidations and esterification with CH_2N_2 to give triester **49** in 84% overall yield without intervening purifications. Selective removal of MEM ether was effected in 94% yield with TMSCl/NaI in MeCN at −23 °C. At this juncture, the C5 tertiary alcohol was protected as its TMS ether *via* two-step bissilylation–monodesilylation sequence to give alcohol **50**, which upon treatment with Dess–Martin periodinane furnished aldehyde **51**.

To install the C1 alkyl side chain, initial attempts to employ Grignard reagent **35** (M=MgBr) resulted in low yield. We then elected to use alkyne **57** as a C1 alkyl side chain equivalent. Chart 5 summarizes the synthesis of alkyne **57**,[44] starting with the known allyl alcohol **52**.[45] Catalytic asymmetric epoxidation of **52** under Sharpless conditions[46] provided epoxy alcohol **53** in 91% yield and 92% ee. Enantiomeric excess could be enhanced to 100% upon recrystallization of the derived 3,5-dinitrobenzoate **54**. Transesterification of **54** with MeOH reproduced the enantiomerically pure epoxy alcohol **53** in 96% yield. After interim protection of the hydroxyl group in **53** as an MPM ether, regioselective opening of the epoxide could be achieved with Me_3Al in the presence of a catalytic amount of BuLi[47] to give alcohol **55** in 92% yield. Methanesulfonylation of **55**, followed by deprotection of the MPM ether and exposure to methanolic potassium carbonate, afforded volatile epoxide **56** in 87% yield. A regioselective ring-opening of **56** with lithium acetylide according to the Yamaguchi protocol[48] and subsequent protection of the liberated alcohol as a benzyl ether then provided alkyne **57** in 95% yield.

As anticipated, installation of the C1 alkyl side chain was uneventfully achieved by the addition of the lithium acetylide

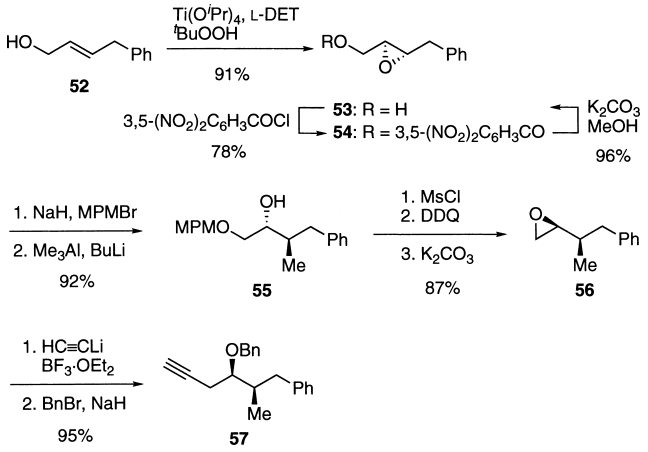


Chart 5. Synthesis of the C1 Alkyl Side Chain Equivalent **57**

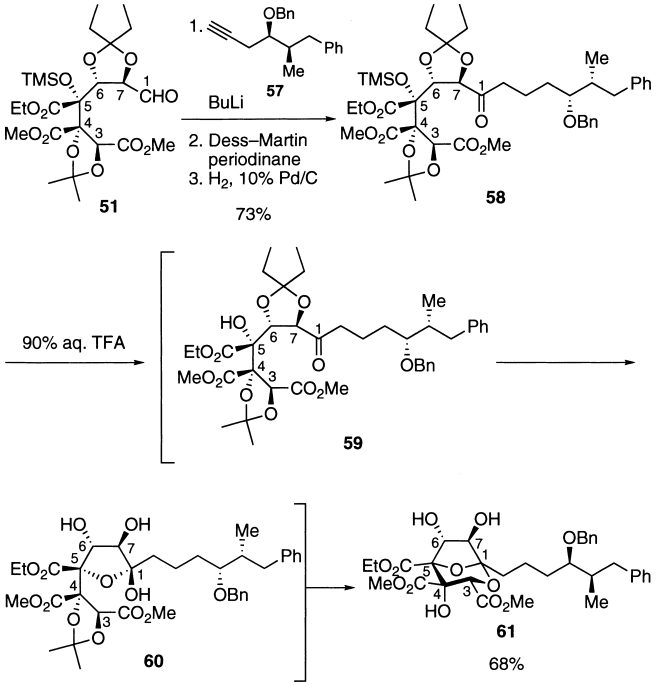


Chart 6. Installation of the C1 Alkyl Side Chain and Internal Ketalization

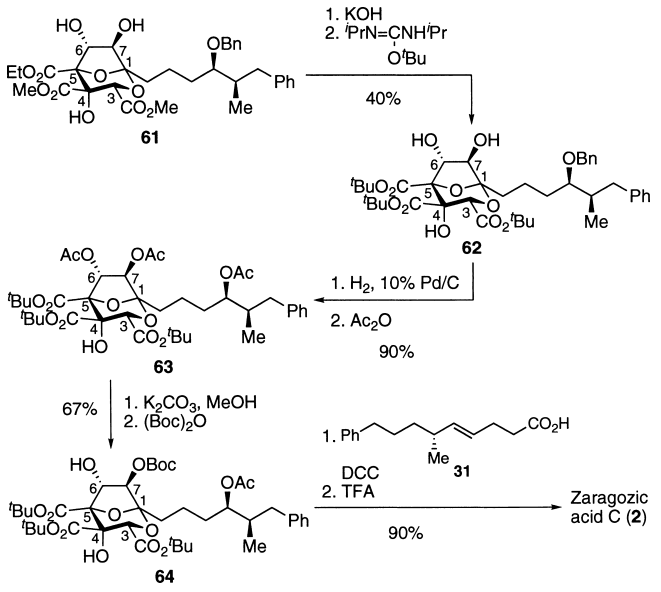


Chart 7. Completion of the Total Synthesis of Zaragozic Acid C (**2**)

derived from alkyne **57** to aldehyde **51** (Chart 6). Dess–Martin oxidation followed by catalytic hydrogenation of a triple bond furnished ketone **58** in 73% yield. Having successfully arrived at the cyclization precursor **58**, attention was directed toward the crucial internal ketalization. Exposure of **58** to 90% aqueous TFA resulted in removal of protecting groups and concomitant ketalization, affording bicycloketal **61** in 68% yield. Monitoring of this reaction by TLC analysis showed that desilylation took place immediately to form hydroxyketone **59**, from which the pentylidene ketal was subsequently removed to give five-membered hemiketal **60** through closure of the C5 hydroxyl group onto the C1 carbonyl. The acetonide required 15 h to be completely hydrolyzed, providing the desired bicycloketal **61** as a single stereoisomer. These observations suggest that the selectivity in the internal ketalization process was mainly due to the differential rates of protecting group hydrolysis.[31,32] To avoid concomitant hydrolytic cleavage of the C6 acyl side chain at the end of the synthesis, triesters present in **61** were hydrolyzed and reacted with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea[49] to give tris(*tert*-butyl) ester **62** in 40% yield (Chart 7). Debenzylation was followed by peracetylation to produce triacetate **63** in 90% yield. The route to **63** constitutes a formal synthesis of zaragozic acid C (**2**) since it intersects the same intermediate employed by Carreira and Du Bois.[24,25] Following a strategy developed by Carreira, selective removal of the C6 and C7 acetyl groups, selective protection of C7 hydroxyl group with $(Boc)_2O$, coupling with **31**,[11] and global deprotection gave zaragozic acid C (**2**) in 60% overall yield. Although the total synthesis of zaragozic C has been accomplished in 30 steps and 1.2% overall yield from diethyl L-tartrate, our synthesis incurs a stereochemical problem at C5 in the key fragment assembly aldol process. It also became apparent that the strategy would not be amenable to the synthesis of the core-modified analogues. We felt compelled to develop a second-generation synthesis of zaragozic acids through an entirely distinct route.

4. Tandem Carbonyl Ylide Formation/1,3-Dipolar Cycloaddition Approach to Zaragozic Acid C

4.1. Tandem Carbonyl Ylide Formation/1,3-Dipolar Cycloaddition Sequence When a diazo functionality located at the suitable position relative to a carbonyl group of a substrate is exposed to an appropriate transition metal catalyst, generation of a metallocarbenoid is followed by an intramolecular attack of the Lewis basic oxygen of the carbonyl group, producing a cyclic carbonyl ylide as a transient species, which can be trapped through 1,3-dipolar cycloaddition (Chart 8).[50—55] The utility of the method was first demonstrated by Ibata and co-workers in 1972, wherein $Cu(acac)_2$ was used as a catalyst.[56] Since Padwa and coworkers reported that the rhodium(II)-mediated cyclization/cycloaddition reactions proceeded under much milder conditions than was common for the classic method with $Cu(acac)_2$,[57] this process has been extensively studied and has represented an attractive strategy for tetrahydrofuran formation. In particular, intramolecular cycloadditions are amenable to the construction of oxygen-containing poly-

cyclic compounds. The reactions of carbonyl ylides have generally been believed to proceed through the free ylide instead of the metal complex-associated ylide. However, recent reports from Hodgson's[58,59] and our laboratories[60,61] have demonstrated that the enantioselective carbonyl ylide cycloaddition could be realized using chiral dirhodium(II) carboxylates, suggesting that the rhodium(II) catalyst can remain associated with the carbonyl ylide in the cycloaddition step.

4.2. Total Synthesis of Zaragozic Acid C The principal goal of our study was not simply to devise a more efficient, stereocontrolled synthesis of zaragozic acid, but more importantly to develop a unified strategy that would be applicable to the synthesis of core-modified analogues. From the retrosynthetic perspective, we recognized a tetrahydrofuran ring involved in the core structure of zaragozic acids. This observation suggested that the carbonyl ylide formation/1,3-dipolar cycloaddition sequence could be envisioned to form the 2,8-dioxabicyclo[3.2.1]octane ring system of this molecule. The cycloaddition-based retrosynthetic analysis of zaragozic acid C (**2**) is outlined in Chart 9. To enhance the convergency of the assemblage process, we planned to install the full C1 alkyl side chain late in the synthesis. The implementation of this strategy would allow incorporation of a variety of C1 alkyl side chains into a common, fully elaborated intermediate. Bicyclic compound **71** was envisioned to arise from the 1,3-dipolar cycloaddition of cyclic carbonyl ylide **72**, generated from α-diazo ester **73** in the presence of a rhodium(II) catalyst, with a suitable dipolarophile. A disconnection of the C4–C5 bond lead to *tert*-butyl diazoacetate (**74**) and α-keto ester **75**, which can then be traced back to D-tartaric acid.[62] Independent of our study, the two groups of Merck[63] and Hodgson[64—66] pursued carbonyl ylide cycloaddition-based strategies en route to this class of natural products. Koyama and co-workers at Merck reported that $Rh_2(OAc)_4$-catalyzed decomposition of α-diazo-β-keto ester **76** in the presence of vinyloxytrimethylsilane (**77**) resulted in the rapid assembly of a simple model of the core **79**, albeit in poor yield (Chart 10). Hodgson and co-workers demonstrated that treatment of α-diazo ester **80** with metyl glyoxylate (**81**) in the presence of $Rh_2(OAc)_4$ led to the formation of a 12 : 1 : 1 mixture of 6,8-dioxabicyclo[3.2.1]octane derivatives favoring the desired isomer **83**, which upon desilylation and exposure to aqueous TFA in CH_2Cl_2 furnished the 6,7-dideoxysqualestatin core **85** in 26% overall yield (Chart 11).

At the outset of our efforts, exploratory experiments were performed on α-diazo ester **86**[67] instead of **73** due to its ease of preparation (Chart 12). Although electron-rich alkenes such as (*E*)-vinylene diacetate and benzyl vinyl ether proved to be ineffective dipolarophiles, the reaction of **86** with (*E*)-3-hexene-2,5-dione (**87**) under the influence of $Rh_2(OAc)_4$ in refluxing benzene proceeded with complete stereocontrol to give cycloadduct **88** as a single isomer in 47% yield. The exclusive formation of **88** is consistent with reaction through transition state A, wherein the steric repulsion between the electron-withdrawing group in **87** and the C4 substituents is minimized (Fig. 3). However, all of our efforts to convert the C6, C7 diacetyl groups into a diol unit through Baeyer–Villiger oxidation met with failure. Consequently, the judicious selection of dipolarophiles that could result in much higher yields as well as a completed synthesis was crucial to the

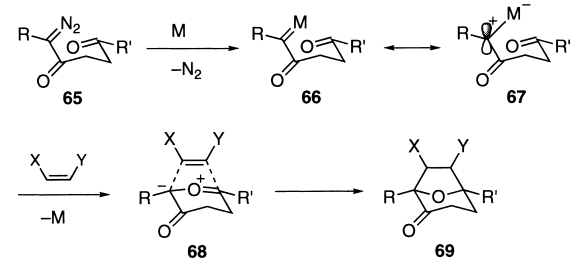


Chart 8. Tandem Carbonyl Ylide Formation and 1,3-Dipolar Cycloaddition

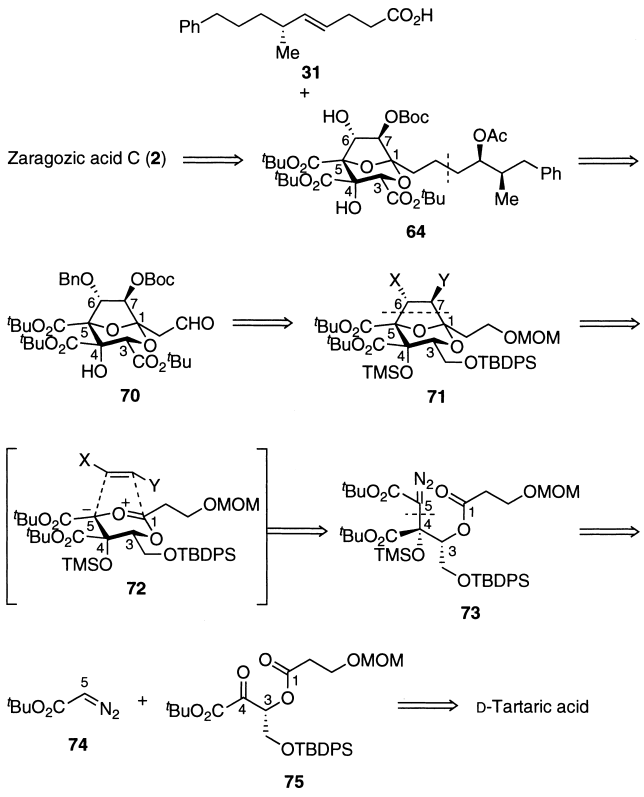


Chart 9. Retrosynthetic Analysis of Zaragozic Acid C (**2**) Based on a Carbonyl Ylide Cycloaddition Strategy

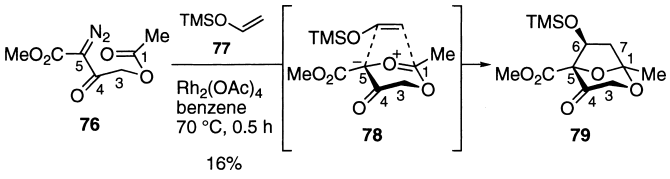


Chart 10. Carbonyl Ylide Cycloaddition Approach to L-740,758, an Oxidative Photodegradation Product of Zaragozic Acid A (**1**)

success of our scenario.

After extensive screening of dipolarophiles, we found that a variety of monosubstituted, electron-deficient alkynes and alkenes could be trapped by the ester-carbonyl ylide intermediate **89**, producing cycloadducts in good yields with complete regio and diastereofacial selectivity (Table 2). Of the various partners tested, 3-butyn-2-one was chosen as the dipolarophile most likely to lead to the completed synthesis.

Having established a viable route to cycloadduct **90**, efforts were next focused on the synthesis of α-diazo *tert*-butyl

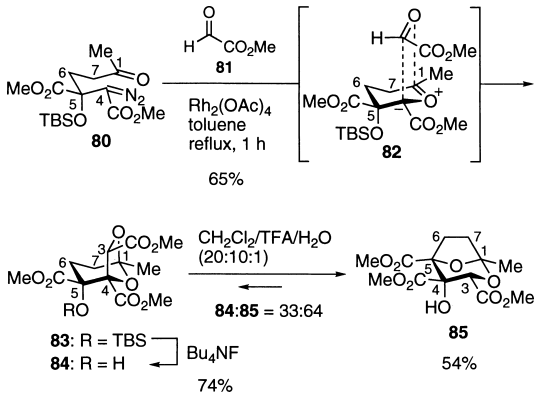


Chart 11. Synthetic Studies of Zaragozic Acids *via* a Carbonyl Ylide Cycloaddition–Rearrangement Strategy

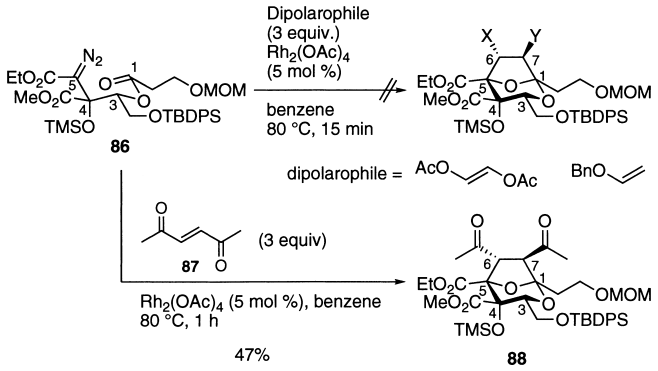


Chart 12. 1,3-Dipolar Cycloaddition of the Carbonyl Ylide Generated from α-Diazo Ester **86**

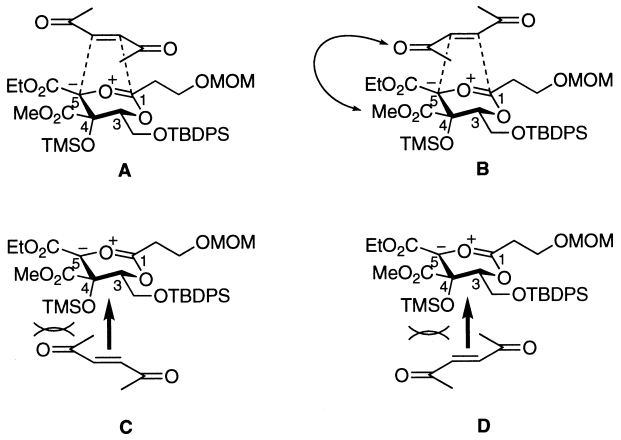
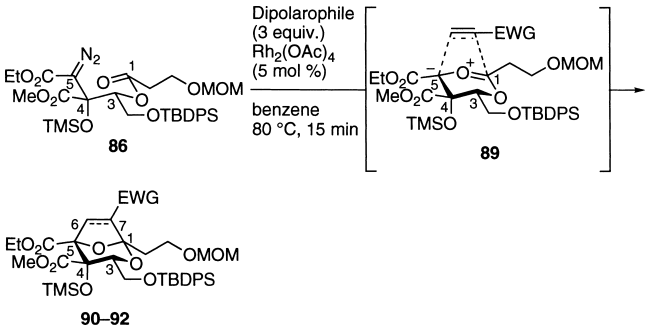
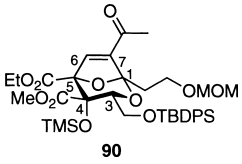
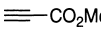
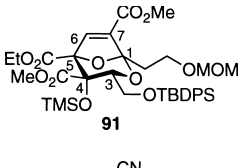
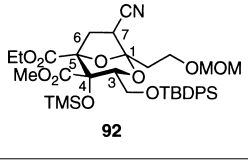


Fig. 3. Stereochemical Course of 1,3-Dipolar Cycloaddition

ester **73**. The synthesis began with the monoprotection of di-*tert*-butyl D-tartrate (**93**)[69] with MPMBr *via* the stannylene acetal, affording MPM ether **94** in 92% yield (Chart 13). At this point, the synthetic plan called for the selective reduction of one of the *tert*-butyl esters in **94**. After considerable experimentation, $LiBH_4$ proved to be the optimal choice for this purpose. Thus $LiBH_4$ reduction of **94** followed by aqueous work-up afforded the aldehyde, which was reduced again with $LiBH_4$ to give 1,3-diol **96** in 72% yield, along with 2% of the 1,2-diol. This highly beneficial result can be rationalized by assuming the predominant formation of a rigid, six-membered boronate intermediate **95** that is resistant to further reduction. Selective silylation of the primary hydroxyl group with TBDPSCl was followed by protection of the remaining secondary alcohol with DHP and deprotection of the MPM ether with DDQ to give alcohol **97** in 88% yield. Acylation of **97** with 3-(methoxymethyl)oxypropionic acid, followed by exposure to TsOH in MeOH, provided alcohol **98** in 74% yield, which underwent Dess–Martin oxidation to afford α-keto ester **75** in 97% yield. At this stage, the crucial diastereoselective addition of metalated *tert*-butyl diazoacetate to **75** was investigated. After a number of unfruitful attempts, we were pleased to find that the use of NaHMDS as a base in CH_2Cl_2/THF (20 : 1) at −93 °C led to acceptable diastereoselectivity (8 : 1), affording the desired α-diazo ester **99** in 65% yield after removal of its C4 epimer. It is noteworthy that the choice of CH_2Cl_2 as a co-solvent, which is not normally used in this type of reaction, was crucial to a high order of selectivity. Protection of the resultant hydroxyl group with HMDS completed the synthesis of the carbonyl ylide precursor **73**.

Table 2. $Rh_2(OAc)_4$-Catalyzed 1,3-Dipolar Cycloaddition of α-Diazo Ester **86**



Dipolarophile	Cycloadduct	Yield (%)
	 **90**	85
	 **91**	82
	 **92**	7α 31 7β 44

Utilizing conditions employed on compound **86**, reaction of α-diazo ester **73** with 3-butyn-2-one in the presence of $Rh_2(OAc)_4$ provided cycloadduct **100** as a single isomer in 72% yield (Chart 14). In accordance with our plan to delay the introduction of the C1 alkyl side chain until the latest possible stage, we then proceeded to the installation of the C6,C7-*trans*-diol unit. Dihydroxylation of enone **100** with OsO_4 proceeded in accordance with the facial bias of the C6–C7 double bond, affording diol **101** in 88% yield, which

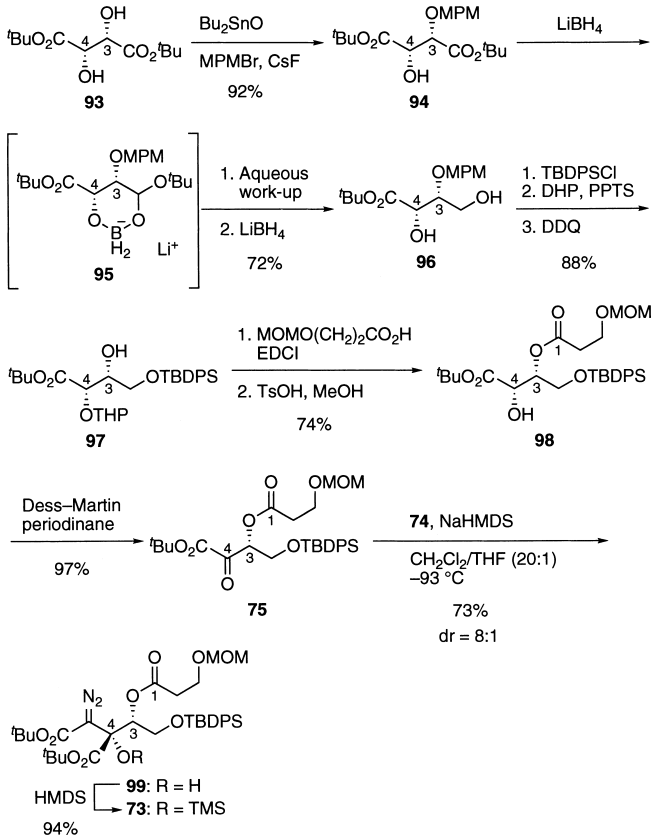


Chart 13. Synthesis of the Cyclization Precursor **73**

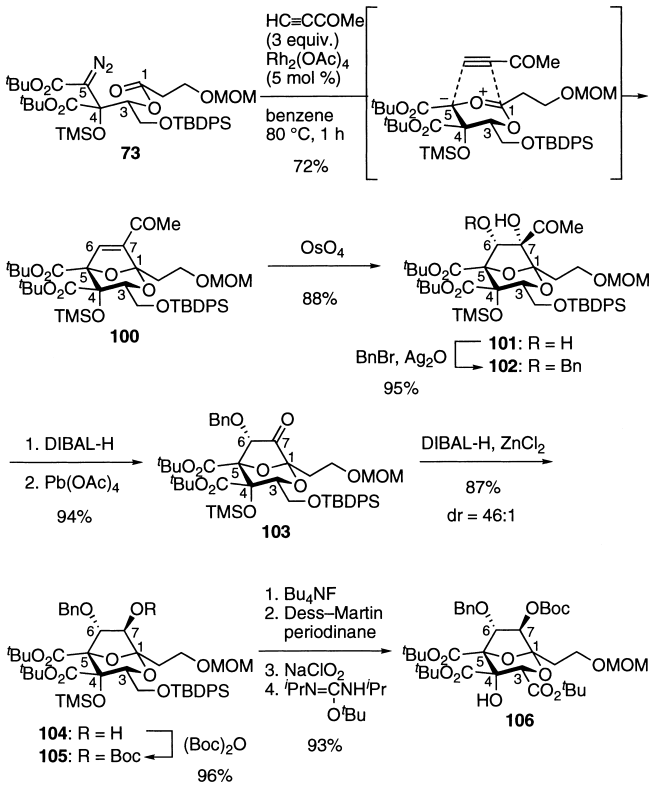


Chart 14. Construction of the Fully Functionalized Bicyclic Compound **106**

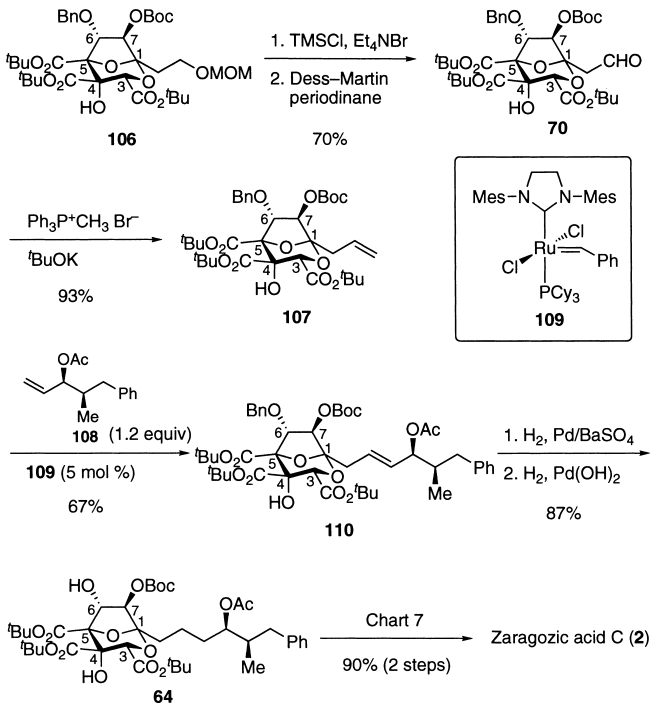


Chart 15. Completion of the Second-Generation Synthesis of Zaragozic Acid C (**2**)

underwent selective benzylation of the hydroxyl group at C6 to give **102** in 95% yield. The superfluous C7 acetyl group was then removed with DIBAL-H reduction and oxidative cleavage of the 1,2-diol with $Pb(OAc)_4$. Of the hydride reducing agents surveyed, DIBAL-H in the presence of $ZnCl_2$ proved most effective in securing the desired alcohol stereochemistry at C7 (dr=46 : 1). The selection of a benzyl protecting group for the C6 alcohol was crucial to the maximum efficiency of these transformations, particularly in terms of essentially perfect selectivities for its installation and C7 carbonyl reduction. The resultant C7 hydroxyl group was protected with $(Boc)_2O$ to give **105** in 96% yield. Desilylation of **105** with Bu_4NF, followed by oxidations and esterification with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea gave the fully functionalized core **106** in 93% yield.

With the bicyclic core successfully functionalized, the remaining operations necessary for the total synthesis involved elongation of the C1 alkyl side chain, followed by installation of the C6 acyl side chain. As a prelude to installing the full C1 side chain, removal of the MOM ether with $TMSCl/Et_4NBr$[70] was followed by Dess–Martin oxidation to provide aldehyde **70** in 70% yield (Chart 15). Since initial attempts to adapt the Kocieński–Julia olefination[71] to this task met with failure, we were then attracted to the viability of a terminal olefin cross-metathesis.[72,73] The terminal olefin was uneventfully incorporated by a Wittig reaction with methylene-triphenylphosphorane to give **107** in 93% yield. Gratifyingly, the cross-metathesis reaction between **107** and **108**[74] with the second-generation Grubbs catalyst (**109**) in benzene at 70 °C provided the desired cross-product **110** in 67% yield. Hydrogenation of the resultant C2′–C3′ double bond without concomitant reductive cleavage of the allylic acetoxy group was followed by debenzylation to afford tris(*tert*-butyl) ester **64**, which was identical in all respects to the intermediate reported previously.[25,38] The conversion of **64** to zaragozic acid C (**2**) has already been described above (Chart

7), thereby completing the second-generation synthesis. The synthesis proceeded in 30 steps for the longest linear sequence, with an improved overall yield of 3.7%.

5. Conclusion

This review covers our efforts that culminated in two total syntheses of zaragozic acid C. Although our first-generation synthesis incurs a stereochemical problem at C5 in the key fragment assembly aldol process, we found that the contiguous quaternary stereocenters could be formed simultaneously in a single operation, and the selectivity in the internal ketalization process was mainly due to the differential rates of protecting group hydrolysis. The successful realization of a second-generation synthesis according to the carbonyl ylide formation/1,3-dipolar cycloaddition process described herein demonstrates the power of such tandem reactions in organic synthesis and such reactions will find continuing application. Importantly, the strategy is flexible with other types of ylides and potentially allows for the introduction of a variety of nonnatural heteroatomic substituents into the core structure.[76)]

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