Natural Products Total Synthesis

Total Synthesis of the Squalene Synthase Inhibitor Zaragozic Acid C by a Carbonyl Ylide Cycloaddition Strategy**

*Seiichi Nakamura, Yuuki Hirata, Takahiro Kurosaki, Masahiro Anada, Osamu Kataoka, Shinji Kitagaki, and Shunichi Hashimoto**

The zaragozic acids and squalestatins, a novel family of fungal metabolites isolated and characterized by researchers at Merck[1] and Glaxo,[2] respectively, in 1992, are the most potent inhibitors of squalene synthase known to date.[3] Some members of this family have also demonstrated the ability to inhibit Ras farnesyl transferase.[4] These molecules share a unique 4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core with six contiguous stereogenic centers and differ only with regard to the nature of the C1 alkyl and C6 O-acyl side chains. It is therefore not surprising that the zaragozic acids (squalestatins) have elicited considerable attention from synthetic chemists.[5] Apart from an enormous number of synthetic studies, eight total syntheses, including our own total synthesis of zaragozic acid C, have now been reported.[6–8] A strategic point in the synthesis of zaragozic acids lies in the construction of the fully or partially functionalized 2,8-dioxabicyclo[3.2.1]octane core structure. The majority of the reported synthetic strategies rely on the acid-catalyzed internal ketalization of a polyhydroxyketone or its equivalent under kinetically or thermodynamically controlled conditions. However, this key reaction often yields, apart from the target bicyclic ketal core, variable quantities of the isomeric 6,8-dioxabicyclo[3.2.1]octane ring. Departing from the ketalization-based approach, we now report a second-generation synthesis of zaragozic acid C capitalizing on the tandem carbonyl ylide formation/1,3-dipolar cycloaddition methodology extensively studied by the Padwa group.[9–11]

Our synthetic strategy based on the cycloaddition of a carbonyl ylide is outlined retrosynthetically in Scheme 1.[12–14] This approach would allow for the rapid assembly of the desired core system from α-diazo ester **3** and a suitable dipolarophile under the influence of a Rh^{II} catalyst in a single step, wherein the problem of formation of the isomeric ketal can be avoided. We have previously demonstrated that

[*] Prof. Dr. S. Hashimoto, Dr. S. Nakamura, Y. Hirata, T. Kurosaki, Dr. M. Anada, Dr. O. Kataoka, Dr. S. Kitagaki
Graduate School of Pharmaceutical Sciences
Hokkaido University
Sapporo 060-0812 (Japan)
Fax: (+81) 11-706-3236
E-mail: hsmt@pharm.hokudai.ac.jp

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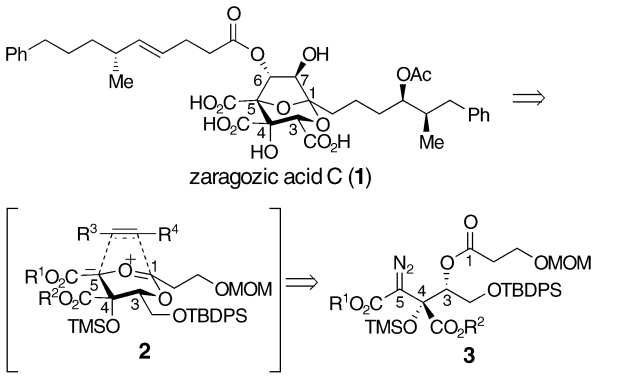
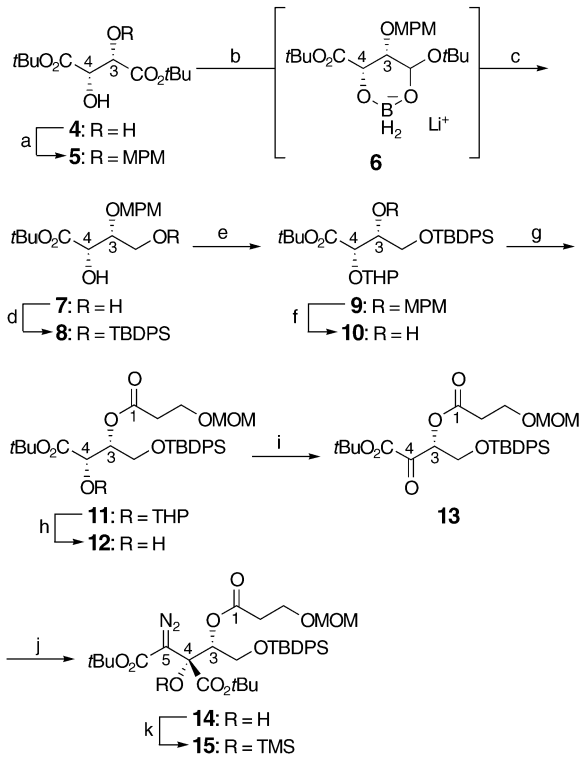


Scheme 1. Retrosynthetic analysis of zaragozic acid C (**1**) based on the cycloaddition of a carbonyl ylide. MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

$Rh_2(OAc)_4$-mediated formation of the carbonyl ylide from α-diazo ester **3** (R^1 = Et, R^2 = Me) and subsequent 1,3-dipolar cycloaddition with (*E*)-3-hexene-2,5-dione as a dipolarophile proceeded with complete stereocontrol to give the desired core structure as a single isomer in 47% yield.[12] However, all of our efforts to convert the C6, C7 diacetyl groups into a diol unit by 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 success of our scenario.

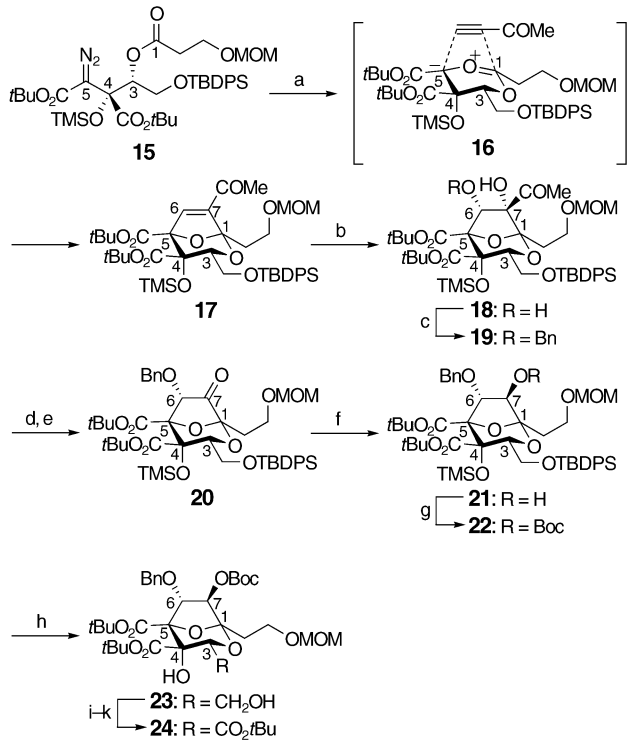
Considering our previous finding that saponification and *tert*-butyl esterification at a later stage were problematic,[7d] we initiated the second-generation synthesis with protection of di-*tert*-butyl D-tartrate (**4**)[15] as its mono-MPM ether to give **5** in 92% yield (Scheme 2, see scheme legends for abbreviations). At this point, the synthetic plan called for the selective reduction of one of the *tert*-butyl esters in **5**.[16] After considerable experimentation, $LiBH_4$ proved to be the optimal choice for this purpose. Thus $LiBH_4$ reduction of **5** followed by aqueous workup afforded the aldehyde, which was reduced again with $LiBH_4$ to give 1,3-diol **7** 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 **6** that is resistant to further reduction. Protective-group manipulations and subsequent oxidation proceeded uneventfully to give α-keto ester **13** in 63% yield, without any racemization over six steps from 1,3-diol **7**. Our effort was then directed toward the addition of metalated *tert*-butyl diazoacetate to **13** to set up the quaternary center at C4, which posed the serious problem of stereocontrol. After a number of unfruitful attempts, we were very 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 **14** in 65% yield after removal of its C4 epimer. It is noteworthy that the choice of CH_2Cl_2 as a cosolvent, which is not normally used in this type of reaction, was crucial to the high level of selectivity,[17] though the reason for this is not clear at present. The synthesis of the carbonyl ylide precursor **15** was then accomplished by TMS-protection of the C4 hydroxy group.

The stage was now set for the crucial tandem formation of the carbonyl ylide and 1,3-dipolar cycloaddition (Scheme 3).



Scheme 2. Synthesis of α-diazo ester **15**. a) Bu_2SnO, toluene, reflux, 2 h, then CsF, MPMBr, DMF, 10 h, 92%; b) $LiBH_4$, THF, 4 h; c) $LiBH_4$, THF, −78 °C, 4 h, 74% (2 steps), 31:1 regioselectivity; d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 30 min, 97%; e) DHP, PPTS, CH_2Cl_2, 5 h, 95%; f) DDQ, CH_2Cl_2, pH 7 buffer, 2 h, 96%; g) MOMO$(CH_2)_2CO_2H$, EDCI, DMAP, CH_2Cl_2, 3 h, 81%; h) TsOH, MeOH, 40 min, 91%; i) Dess–Martin periodinane, CH_2Cl_2, 2 h, 97%; j) N_2CHCO_2tBu, NaHMDS, CH_2Cl_2/THF (20:1), −93 °C, 5 min, 73%, 8:1 diastereoselectivity; k) HMDS, imidazole, THF, 48 h, 94%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DHP = 3,4-dihydro-2*H*-pyran, DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HMDS = 1,1,3,3-hexamethyldisilazane, MPM = 4-methoxybenzyl, PPTS = pyridinium *p*-toluenesulfonate, THP = tetrahydropyranyl, Ts = *p*-toluenesulfonyl.

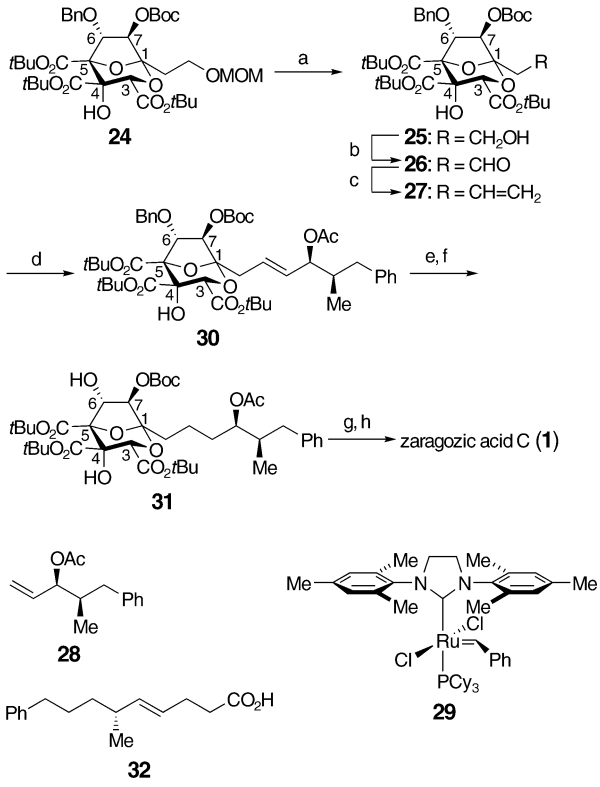
With respect to the dipole reactivity of this type of ester-carbonyl ylide, we previously reported that the most dominant interaction of the frontier molecular orbitals (FMOs) is between the HOMO of the ester-carbonyl ylide and the LUMO of an electron-deficient dipolarophile.[12] The reaction was conducted by adding over one hour a solution of α-diazo ester **15** in benzene to a solution of $Rh_2(OAc)_4$ (5 mol%) and a dipolarophile candidate (3 equiv) in benzene heated at reflux. Apart from the dipolarophiles activated with two carbonyl groups described in the previous studies, we now found that a variety of α,β-ethylenic and α,β-acetylenic carbonyl compounds could be smoothly trapped by the ester-carbonyl ylide intermediate **16**. Furthermore, this reaction occurred exclusively from the β-face of the ylide so as to avoid the C4 pseudoaxial trimethylsilyloxy group on the opposite face. Of the various partners tested,[18] 3-butyn-2-one was chosen as the dipolarophile to most likely lead to the completed synthesis (vide infra); the desired cycloadduct **17** was obtained as a single diastereomer in 72% yield.[19] We



Scheme 3. Construction of the fully functionalized bicyclic compound **24**. a) $Rh_2(OAc)_4$ (5 mol%), HC≡CCOMe (3 equiv), benzene, reflux, 1 h, 72%; b) OsO_4, NMO, aq acetone, 20 h, 88%; c) BnBr, Ag_2O, DMF, 48 h, 95%; d) DIBAL-H, toluene, −78°C, 30 min, quant.; e) $Pb(OAc)_4$, benzene, 30 min, 94%; f) DIBAL-H, $ZnCl_2$, CH_2Cl_2, −78°C, 0.5 h, 87%, 46:1 diastereoselectivity; g) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, 2 h, 96%; h) Bu_4NF, THF, 0°C, 30 min, 97%; i) Dess–Martin periodinane, CH_2Cl_2, 24 h; j) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq *t*BuOH, 3 h; k) *i*PrN=C(O*t*Bu)NH*i*Pr, CH_2Cl_2, 24 h, 96% (3 steps). Bn = benzyl, Boc = *tert*-butoxycarbonyl, DIBAL-H = diisobutylaluminum hydride, NMO = 4-methylmorpholine *N*-oxide.

then proceeded to the installation of the C6, C7-*trans*-diol unit. Dihydroxylation of enone **17** with OsO_4 proceeded in accord with the facial bias of the C6–C7 double bond, affording diol **18** in 88% yield. Selective benzylation of the C6 hydroxy group furnished α-hydroxyketone **19**,[20] which was then converted into ketone **20** in 89% overall yield by DIBAL-H reduction and oxidative cleavage of the 1,2-diol with $Pb(OAc)_4$. In the next step, reduction of the C7 carbonyl group in **20**, we encountered serious difficulties in stereocontrol. After an exhaustive survey of reducing agents and solvents, it was found that this goal could best be achieved with DIBAL-H/$ZnCl_2$[21] in CH_2Cl_2 to give the desired alcohol **21** and its C7 epimer recyclable in 87% yield with excellent diastereoselectivity (46:1). It is noteworthy that the choice of the *O*-benzyl protecting group at C6 was crucial to the maximum efficiency of these transformations, particularly in terms of essentially perfect selectivities for its installation and C7 carbonyl reduction. Protection of the C7 hydroxy group with $(Boc)_2O$ and subsequent bisdesilylation with Bu_4NF provided diol **23** in 93% yield, which, upon the three-step sequence without intervening purifications, gave tris(*tert*-butyl) ester **24** in 96% yield.

The remaining portion of the synthesis required elongation of the C1 alkyl side chain followed by installation of the C6 acyl side chain. Removal of the MOM ether in **24** with TMSCl/Et_4NBr[22] was followed by oxidation with Dess–Martin periodinane to give aldehyde **26** in 70% yield (Scheme 4).



Scheme 4. Completion of the total synthesis of **1**. a) TMSCl, Et_4NBr, CH_2Cl_2, 20 h, 75%; b) Dess–Martin periodinane, CH_2Cl_2, 24 h, 93%; c) $Ph_3P^+CH_3Br^-$, *t*BuOK, toluene, 40°C, 30 min, 91%; d) **28** (1.2 equiv), **29** (5 mol%), benzene, 70°C, 8 h, 67%; e) H_2, 5% Pd/$BaSO_4$, EtOAc, 10 h; f) H_2, 20% $Pd(OH)_2$/C, EtOAc, 1 h, 87% (2 steps); g) **32**, DCC, DMAP, CH_2Cl_2, 48 h, 90%; h) TFA, CH_2Cl_2, 16 h, quant. Cy = cyclohexyl, DCC = dicyclohexylcarbodiimide, TFA = trifluoroacetic acid.

At this stage, we encountered a final key problem: how to install the full C1 side chain. Since initial attempts to adapt the Kocieński–Julia olefination[23] to this task met with failure, we were then attracted to the viability of the cross-metathesis of a terminal olefin.[24] Indeed, we were gratified to find that the cross-metathesis coupling between the terminal olefin **27** derived from **26** and allyl acetate **28**[25] (1.2 equiv) in benzene in the presence of 5 mol% of the second-generation Grubbs catalyst (**29**) at 70°C proceeded remarkably smoothly to give cross-product **30**[27] with exclusive *E* stereochemistry in 67% yield, along with recovered alkenes **27** (10%) and **28** (24%). As might be expected from the sterically hindered nature of the olefinic functionality adjacent to the core system, the dimer arising from self-metathesis of **27** was not detected. Hydrogenation of the C2′–C3′ double bond in **30** without concomitant reductive cleavage of the acetoxy group followed by hydrogenolysis of C6 benzyl ether furnished

tris(*tert*-butyl) ester **31** in 87% yield. Compound **31** was identical in all respects (^{1}H NMR, ^{13}C NMR, IR, HRMS, $[\alpha]_D$) to the intermediate previously prepared by both the Carreira group[7b] and our group.[7d] Thus, acylation of the hydroxy group at C6 with (*R*)-9-phenyl-6-methyl-4-nonenoic acid (**32**) and global deprotection with TFA completed the total synthesis of zaragozic acid C (**1**).

In conclusion, we have accomplished a highly convergent and stereocontrolled total synthesis of zaragozic acid C in 30 steps (longest linear sequence) and 3.7% overall yield from di-*tert*-butyl D-tartrate (**4**). The synthesis illustrates the power of the carbonyl ylide cycloaddition methodology for rapidly assembling the unique 2,8-dioxabicyclo[3.2.1]octane core and the olefin cross-metathesis methodology to construct the C1 alkyl side chain. 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. The synthesis of such analogues for biological and pharmacological investigations is currently underway.

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Keywords: carbonyl ylides · cycloaddition · diazo compounds · metathesis · total synthesis

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[18] The following dipolarophiles gave the corresponding cycloadducts: methyl propiolate, 75%; methyl vinyl ketone, 59%; methyl acrylate, 68%; acrylonitrile, 62%.

[19] Product yields obtained with other Rh^{II} complexes: $Rh_2(O\text{-}COC_7H_{15})_4$, 71%; $Rh_2(OCOPh)_4$, 66%; $Rh_2(OCOC_3F_7)_4$, 11%; $Rh_2(NHAc)_4$, 72%.

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1) NaOMe, MeOH, then PhSH; 2) MPMBr, NaH, THF–DMF; 3) *m*CPBA, CH_2Cl_2, −25 °C; 4) TFAA, pyridine, CH_2Cl_2, 0 °C, then $NaHCO_3$, MeOH; 5) $Ph_3P{=}CH_2$, THF, 0 °C; 6) DDQ, aq CH_2Cl_2; 7) Ac_2O, pyridine, DMAP, CH_2Cl_2. *m*CPBA = 3-chloroperoxybenzoic acid, TFAA = trifluoroacetic anhydride.

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