Pergamon

Tetrahedron Letters 39 (1998) 2371–2374

TETRAHEDRON LETTERS

Toward the Second-Generation Synthesis of Zaragozic Acids: Construction of the 2,8-Dioxabicyclo[3.2.1]octane Core System *via* Tandem Carbonyl Ylide Formation and 1,3-Dipolar Cycloaddition Sequence

Osamu Kataoka,[1] Shinji Kitagaki, Nobuhide Watanabe, Jun-ichi Kobayashi, Sei-ichi Nakamura, Motoo Shiro,[†] and Shun-ichi Hashimoto*

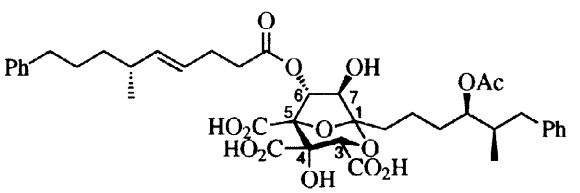
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

[†]Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196, Japan

Received 25 December 1997; revised 14 January 1998; accepted 16 January 1998

Abstract: *A highly efficient construction of the 2,8-dioxabicyclo[3.2.1]octane core structure of zaragozic acids, inhibitors of the enzyme squalene synthase, has been achieved by exploiting the sequence of rhodium(II)-mediated intramolecular carbonyl ylide formation from an α-diazo ester and stereocontrolled 1,3-dipolar cycloaddition with (E)-3-hexene-2,5-dione.*

Elevated serum cholesterol levels have been well established as a key risk factor for the development of atherosclerosis and coronary heart disease.[2] In this connection, the discovery of zaragozic acids and squalestatins by respective researchers at Merck and Glaxo is a notable recent landmark, because this novel family of fungal metabolites has been shown to be picomolar competitive inhibitors of squalene synthase,[2,3] the enzyme involved in the first committed step of the *de novo* cholesterol biosynthetic pathway. Some members of this family have also been found to display Ras farnesyl transferase inhibitory activity.[4] 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 carbons, and represent considerable variations in the C1 alkyl and C6 acyl side chains. Not surprisingly, their biomedical significance coupled with the novel molecular architecture has provided a powerful incentive for numerous synthetic chemists to embark on the synthesis of zaragozic acids (squalestatins) and their analogues. Apart from an enormous amount of synthetic studies, the Nicolaou[5] and Heathcock[6] groups have accomplished the total synthesis of zaragozic acid A (squalestatin S1), while efforts of the groups of Carreira[7] and Evans[8] have culminated in the total synthesis of zaragozic acid C (**1**).[9] Recently, we also have completed the total synthesis of **1** by a convergent strategy, wherein the key feature is a simultaneous creation of the C4 and C5 quaternary carbon centers by $Sn(OTf)_2$-promoted aldol coupling reaction between an α-keto ester and silyl ketene thioacetal derived from L- and D-tartaric acids, respectively.[10] However, our synthesis incurs a stereochemical problem at C5 in the key fragment assembly aldol process. Thus, we have addressed a second-generation synthesis of zaragozic acids, highlighting an alternative construction of the 2,8-dioxabicyclo[3.2.1]octane core system *via* a tandem carbonyl ylide formation and 1,3-dipolar cycloaddition sequence.



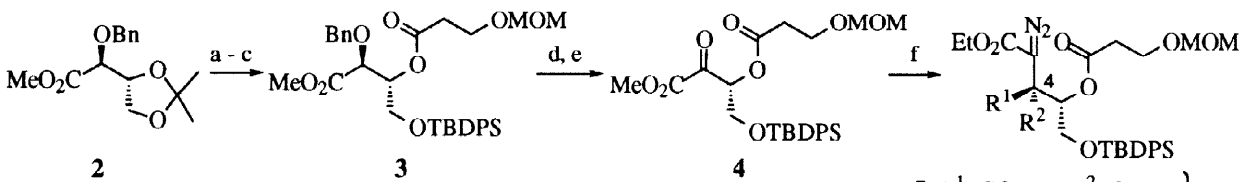
Zaragozic acid C (**1**)

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.[9] The majority of the reported synthetic strategies relies on acid-catalyzed internal ketalization of polyhydroxyketones under kinetically or thermodynamically

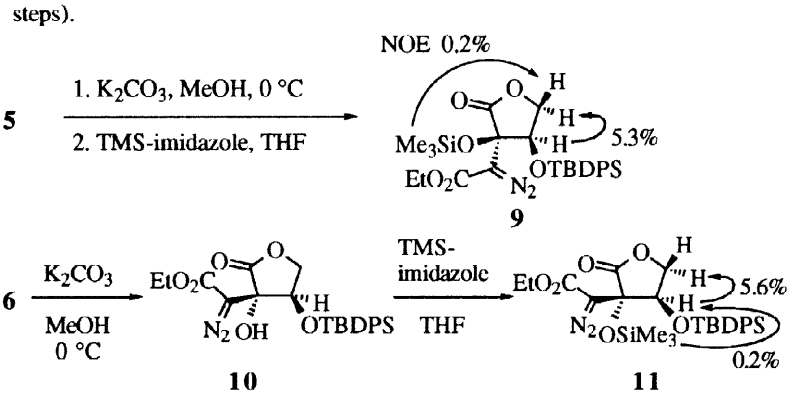
0040-4039/98/$19.00
PII: S0040-4039(98)00203-2

controlled conditions,[11] wherein, apart from the target bicyclic ketal core, there have often been observed variable quantities of the isomeric 6,8-dioxabicyclo[3.2.1]octane ring. Independent of these strategies,[12] Koyama and his coworkers reported a very elegant approach exploiting the tandem cyclization-cycloaddition sequence extensively developed by Padwa,[13] wherein $Rh_2(OAc)_4$-catalyzed decomposition of methyl 4-acetyloxy-2-diazo-3-oxobutyrate in the presence of vinyloxytrimethylsilane or benzyl vinyl ether led to the rapid assembly of a simple model of the zaragozic acid core, albeit in poor yields (16% and 9%, respectively).[12a] In spite of the disappointing precedent, we explored this chemistry with an actual substrate, since assessment of the factors responsible for this process seemed to be ambiguous.[14]

Toward this end, the fully functionalized α-diazo ester **7** was prepared from the readily available acetonide **2**[15] as shown in Scheme 1.[16] Deprotection of the isopropylidene acetal group in **2** was followed by selective silylation of the primary alcohol and acylation of the secondary alcohol with 3-(methoxymethoxy)propionic acid to afford ester **3** in 67% yield. Debenzylation of **3** and subsequent oxidation with the Dess-Martin periodinane furnished α-keto ester **4** in 80% yield. Addition of ethyl lithiodiazoacetate[17] to **4** in THF at -78 °C proceeded smoothly to give a mixture of adducts **5** and **6** in a 1.5:1 ratio, which was silylated and then separated by column chromatography on silica gel to produce the desired α-diazo ester **7** in 40% yield, along with 26% of its C4 epimer **8**. The stereochemical assignments of **7** and **8** were obtained from ^1H NOE experiments of the γ-lactones **9** and **11** derived from **5** and **6**, respectively, *via* deblocking of the acyl group, 1,2-*O*-TBDPS group migration,[18] and ring closure followed by 4-*O*-silylation (Scheme 2). These assignments were further substantiated by the X-ray crystal structure of γ-lactone **10** (Fig. 1).



Scheme 1. *Reagents and conditions:* (a) 10% aq. HCl-THF (1:1), 0 °C, 12 h, 78%. (b) TBDPSCl, pyridine, DMAP, CH_2Cl_2, 20 h, 96%. (c) $MOMO(CH_2)_2CO_2H$, EDCI, DMAP, CH_2Cl_2, 5 h, 89%. (d) H_2, 20% $Pd(OH)_2/C$, MeOH, reflux, 20 h, 85%. (e) Dess-Martin periodinane, CH_2Cl_2, 8 h, 94%. (f) N_2CHCO_2Et, LiHMDS, THF, -78 °C, 3 h. (g) HMDS, imidazole, THF, 14 h, 40% of **7** and 26% of **8** (2 steps).



Scheme 2

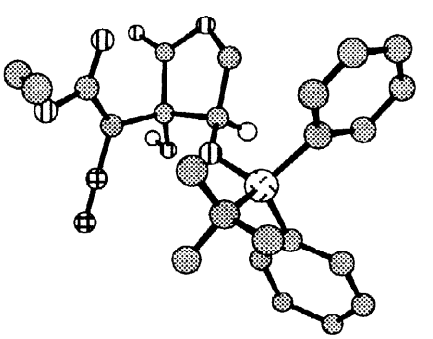
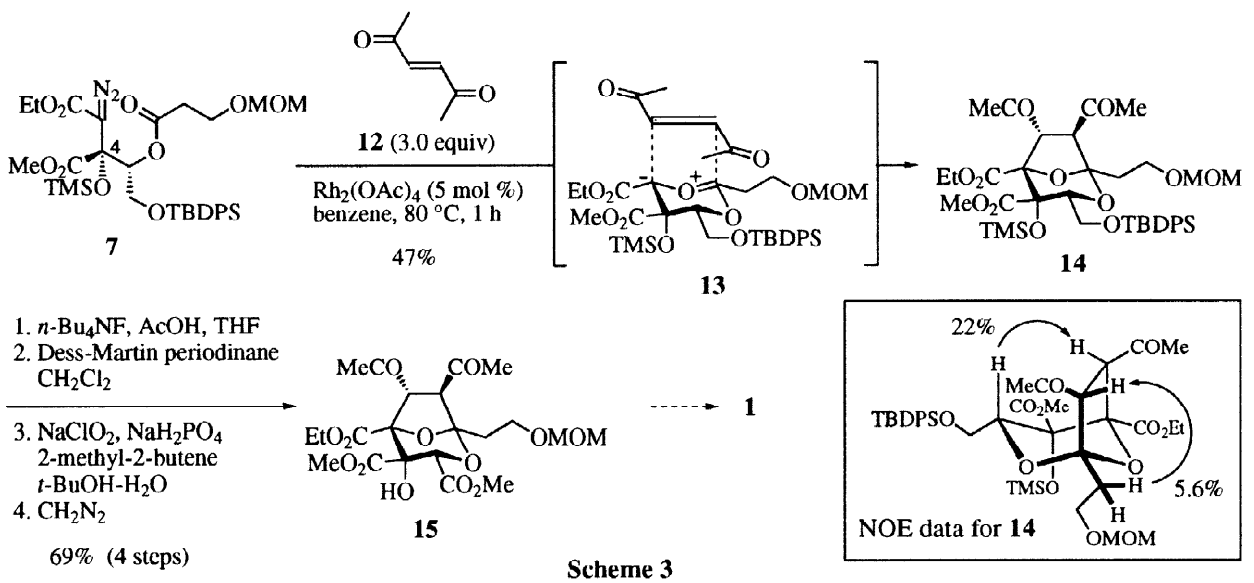


Figure 1. X-ray crystal structure of **10**.

With convenient access to the carbonyl ylide precursor secured, the stage was now set for the tandem cyclization-cycloaddition reaction. The reaction was performed by slowly adding a solution of α-diazo ester **7** in benzene to a refluxing benzene solution of $Rh_2(OAc)_4$ (5 mol %) and a suitable dipolarophile (3 equiv) (Scheme 3). However, a most aggressive attempt to trap the carbonyl ylide **13** generated from **7** by the action of $Rh_2(OAc)_4$ with (*E*)-vinylene diacetate[19] as a 1,2-ethylenediol equivalent met with failure. The use of vinyl acetate also gave none of the cycloadducts. With respect to the dipole reactivity of cyclic carbonyl ylides derived from the α-diazo ketone or α-diazo β-keto ester, it is documented that the most dominant interaction in the former case is between the HOMO of the carbonyl ylide and the LUMO of electron-deficient dipolarophiles,[20]

whereas the most favorable interaction in the latter case is between the LUMO of the carbonyl ylide and the HOMO of electron-rich dipolarophiles.[12a] While little is known about the reaction tendency of carbonyl ylide from α-diazo ester, the above results coupled with the calculations[21] suggested that there is no beneficial involvement of the LUMO (dipole)-HOMO (dipolarophile) interaction here. On the other hand, the calculations predicted that this carbonyl ylide could possess the smallest energy gap between its HOMO and the LUMO of the electron-deficient dipolarophile. Thus, we next chose (*E*)-3-hexene-2,5-dione (**12**)[22] as an electron-deficient 1,2-ethylenediol equivalent. Indeed, we were delighted to find that 1,3-dipolar cycloaddition of **13** with **12** afforded the desired cycloadduct **14** as a single diastereomer out of the four possible diastereomers in 47% yield,[23] the stereochemistry of which was rigorously established by ^{1}H NOE experiment. The great stereochemical outcome of the cycloaddition can be explained as follows; addition of dipolarophile **12** is presumed to proceed exclusively from the β-face of the carbonyl ylide intermediate **13** so as to avoid non-bonding interaction with the C4 pseudoaxial trimethylsilyloxy group in **13**,[24] wherein the activating groups in **12** are nicely accommodated in a less crowded space. In stark contrast, we were surprised to observe that treatment of the undesired α-diazo ester **8** with **12** under the foregoing conditions gave no cycloadduct resulting from carbonyl ylide formation.[25] These results show that the configuration at C4 in α-diazo ester **7** is crucial to the success of the present cycloaddition, though the reason is presently not clear. Since **14** was uneventfully converted to the triester **15**, a remaining key task for the elaboration of the zaragozic acid core system is the Baeyer-Villiger oxidation.



Scheme 3

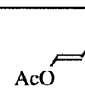
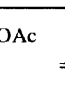
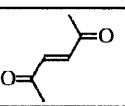
In summary, we have achieved a highly efficient construction of the 2,8-dioxabicyclo[3.2.1]octane core structure of zaragozic acids *via* a tandem cyclization-cycloaddition sequence with complete stereocontrol. Our efforts are currently being focused on the conversion of C6,C7-diacetyl groups to a diol unit.[26]

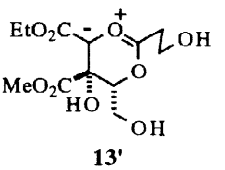
References and Notes

1. Present address: Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan.
2. Biller, S. A.; Neuenschwander, K.; Ponpipom, M. M.; Poulter, C. D. *Curr. Pharm. Des.* **1996**, *2*, 1.
3. Watson, N. S.; Procopiou, P. A. In *Progress in Medicinal Chemistry*; Ellis, G. P.; Luscombe, D. K., Eds.; Elsevier: 1996, Vol. 33, pp. 331-378.
4. Gibbs, J. B.; Pompliano, D. L.; Mosser, S. D.; Rands, E.; Lingham, R. B.; Singh, S. B.; Scolnick, E. M.; Kohl, N. E.; Oliff, A. *J. Biol. Chem.* **1993**, *268*, 7617.
5. Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467.
6. Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126.
7. Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

8. Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111.
9. For reviews, see: (a) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 773. (b) Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622.
10. Sato, H.; Nakamura, S.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 451.
11. For recent synthetic studies of the bicyclic core of zaragozic acids based on acid-catalyzed internal ketalization method, see: (a) Shimizu, A.; Ohmori, K.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Carbohydr. Lett.* **1996**, *1*, 433. (b) Hodgson, D. M.; Bailey, J. M.; Harrison, T. *Tetrahedron Lett.* **1996**, *37*, 4623. (c) Tsubuki, M.; Tomitsuka, K.; Okita, H.; Honda, T. *Symposium Papers of 38th Symposium on the Chemistry of Natural Products*; Sendai, Japan, 1996; p. 601. (d) Xu, Y.; Johnson, C. R. *Tetrahedron Lett.* **1997**, *38*, 1117. (e) Paterson, I.; Feßner, K.; Finlay, M. R. V. *Tetrahedron Lett.* **1997**, *38*, 4301. (f) Hegde, S. G.; Myles, D. C. *Tetrahedron* **1997**, *53*, 11179.
12. (a) Koyama, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185. (b) Freeman-Cook, K. D.; Halcomb, R. L. *Tetrahedron Lett.* **1996**, *37*, 4883.
13. For a review, see: Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.
14. An alternative approach *via* assembly of the 6,8-dioxabicyclo[3.2.1]octane ring by 1,3-dipolar cycloaddition of a carbonyl ylide generated from α-diazo β-keto ester with methyl glyoxylate followed by acid-catalyzed rearrangement has recently been reported.[11b]
15. (a) Ohno, M.; Fujita, K.; Nakai, H.; Kobayashi, S.; Inoue, K.; Nojima, S. *Chem. Pharm. Bull.* **1985**, *33*, 572. (b) Lichtenthaler, F. W.; Jarglis, P.; Lorenz, K. *Synthesis* **1988**, 790.
16. All new compounds exhibited satisfactory spectral (500 MHz ^{1}H NMR and 67.5 MHz ^{13}C NMR) and high resolution mass spectral characteristics.
17. Schöllkopf, U.; Frasnelli, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 301.
18. Mulzer, J.; Schöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431 and references cited therein.
19. Nagasawa, J.; Araki, Y.; Ishido, Y. *J. Org. Chem.* **1981**, *46*, 1734.
20. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
21. Both HOMO and LUMO energies of the dipole **13'** and dipolarophiles were calculated after optimizing the molecular geometry, first using augmented MM2, then using MOPAC with AM1 parameters. The energy separations are presented in Table 1.

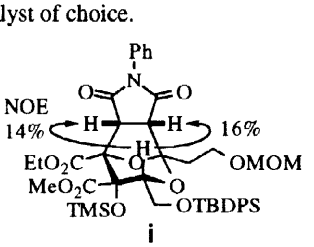
Table 1. HOMO-LUMO energy separation in 1,3-dipolar cycloaddition of ylide **13'** with dipolarophiles

Dipolarophile				DMAD
[HOMO(dipole) – LUMO(dipolarophile)] (eV)	8.71	8.97	7.33	7.06	7.39
[HOMO(dipolarophile) – LUMO(dipole)] (eV)	8.36	8.90	9.77	8.06	10.95

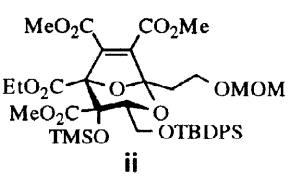


13'

22. Levisalles, J. *Bull. Soc. Chim. Fr.* **1957**, 997.
23. Of the dirhodium(II) catalysts [$Rh_2(O_2CH)_4$, $Rh_2(OAc)_4$, $Rh_2(O_2CC_7H_{15})_4$, $Rh_2(O_2CCPh_3)_4$, $Rh_2(O_2CC_3F_7)_4$ and $Rh_2(NHCOCH_3)_4$] screened, $Rh_2(OAc)_4$ proved to be the catalyst of choice.
24. Cycloaddition of **13** with electron-deficient dipolarophiles such as *N*-phenylmaleimide or dimethyl acetylenedicarboxylate (DMAD) was also found to give cycloadducts **i** and **ii** as a single diastereomer in 61% and 67% yields, respectively. The stereochemistry of **i** was confirmed by ^{1}H NOE experiment, and that of **ii** was assigned by analogy.



i



ii

25. A similar result was obtained with the use of *N*-phenylmaleimide or DMAD.

26. This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports and Culture, Japan and also by the Special Coordination Funds of the Science and Technology Agency of the Japanese Government. The authors thank the Japan Society for the Promotion of Science for Research Fellowships for Young Scientists (to O. K.).