Pergamon

Tetrahedron Letters, Vol. 35, No. 49, pp. 9185-9188, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02068-X

A Novel Synthetic Approach Toward the Zaragozic Acids Core Structure

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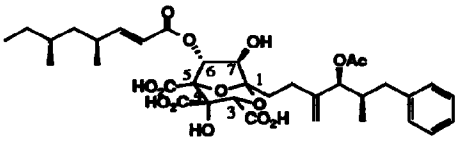
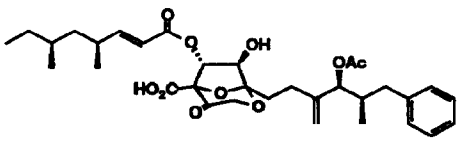
Abstract: A novel synthetic approach toward the zaragozic acids core structure is described. New dipolarophiles in the 1,3-dipolar cycloaddition to the carbonyl ylides are reported. The substituent effect of the dipolarophiles is also discussed.

Zaragozic acid A[1] (squalestatin 1)[2] (1) was discovered as a metabolite from an unidentified sterile fungus (MF5453) and was identified as a potent inhibitor of squalene synthase in recent years. This compound has been actively pursued as a synthetic target because of its potential utility as a cholesterol lowering agent as well as its unique structure.[3] L-740,758[4] (2) was discovered as an oxidative photo-degradation product of zaragozic acid A, and was shown to retain potent activity (IC_{50} 2.5nM). Thus, both compounds 1 and 2 became equally important synthetic targets for us.

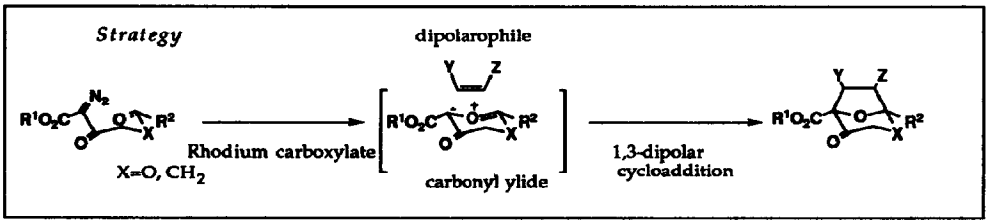


Zaragozic acid A 1



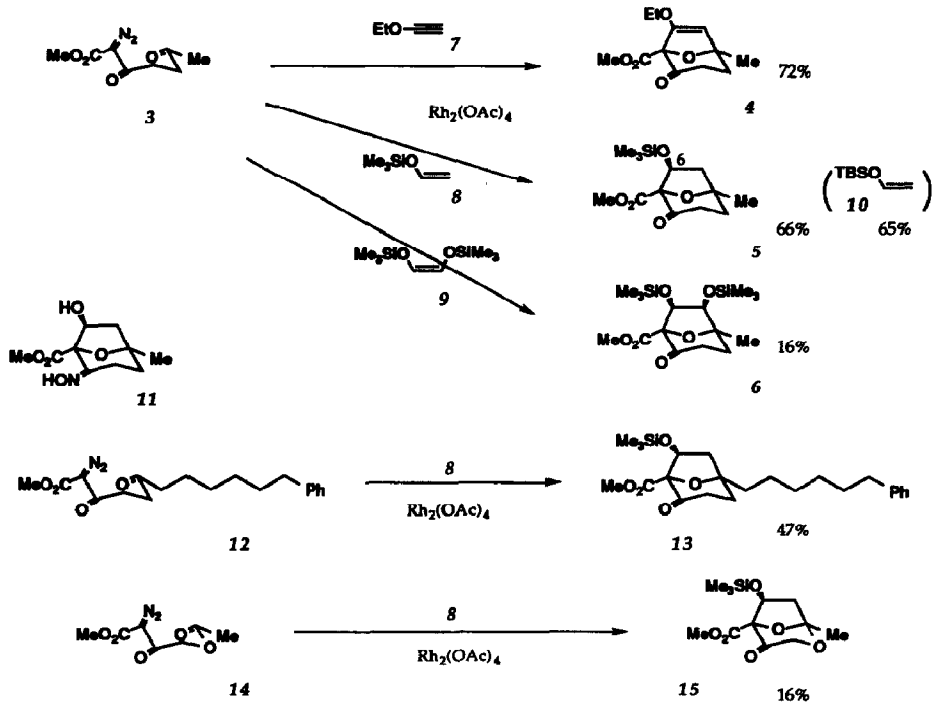
L-740,758 2

The general strategy is shown below. Our approach is based on the tandem cyclization-cycloaddition reaction of dipolarophiles with carbonyl ylides, which has been extensively studied by Padwa's group in recent years.[5] This strategy is advantaged by the swiftness of assembling the bicyclic core structure in a single step.



The diazo substrates for this cyclization-cycloaddition reaction were prepared by standard methods. Successful applications of this key reaction are shown in the scheme. Thus, a dilute benzene solution of the diazo compound was slowly added to the pre-heated (70° C) benzene solution of the dipolarophile and a catalytic amount of rhodium acetate. In most cases, the reaction was complete within 1/2 hr. Subsequent removal of the solvent and purification by silica gel chromatography gave the desired product. In all of the cases in the scheme, the reaction proceeded regio-, and stereoselectively giving a single cyclization-cycloaddition product from each reaction. The stereochemistry of the C6-hydroxyl group was determined by NOESY spectrum (**5**, **6**, **15**).[6] The structure of **5** was confirmed by a single-crystal X-ray analysis of a crystalline derivative **11**.[7]

Scheme

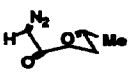
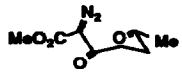
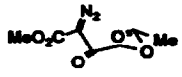


These are the first examples of vinyloxytrialkylsilanes and an alkoxyacetylene[8] as dipolarophiles in this cyclization-cycloaddition reaction. As well, conversion of **14** to **15** is the first report of a dipolarophile reacting with the carbonyl ylide generated between a diazoketone and an aliphatic ester forming a six-membered acetal.[5d, 1] Although the cases yielding the "carbocyclic version" of the core structure went smoothly in general (**4**, **5**, **6**, **13**), the low yield for formation of **15** with an oxygen in the 2-position was rather disappointing.

Surprisingly, the most commonly used dipolarophiles in the literature gave only poor results with our diazoketoester substrates **3** and **14**. Many cases in the literature generated the dipole from diazoketones such as **16**[5e] (see Table). In our studies, electron-rich dipolarophiles such as vinyloxytriaklylsilanes and an alkoxyacetylene gave the most successful results with diazoketoesters. Relatively electron-deficient dipolarophiles such as methylacrylate or methylpropiolate failed or gave only poor results with diazoketoesters, even though they added smoothly to the carbonyl ylide derived from diazoketone **16**.

Conversely, these electron-rich dipolarophiles did not give good results with diazoketone **16**. This striking contrast prompted us to investigate the matching/mis-matching of the dipolarophiles and the carbonyl ylides. The results of the addition of the dipolarophiles to the carbonyl ylides were summarized in the table. Dipolarophiles were classified as acetylenes, olefins, and aldehydes. Isolated yields and the products of the reaction were shown. As the dipolarophile becomes more electron-rich, it reacts better with **3**, and poorly with **16**. It is noteworthy that the order of dipolarophile reactivity switches depending on the presence or absence of an extra carboxyl group on the dipole.

Table Yields and the products of the cyclization-cycloaddition reaction

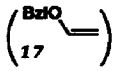
substrates   

16 *3* *14*

(a) Acetylenic dipolarophiles

isolated yield % (products)

dipolarophile / substrate	EtO—≡	≡—CO_2Me
16	17% (18)	80% (19, 20)
3	72% (4)	16% (21)



17

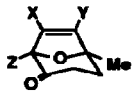
(b) Olefinic dipolarophiles

dipolarophile / substrate	TMSO—	BzlO—	AcO—	MeO_2C—
16	16% (22)	15% (23)	40% (24)[5e]	90% (25, 26)[5e]
3	66% (5)	48% (27)	0%	0%
14	16% (15)	9% (28)		

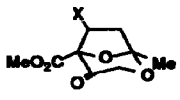
(c) Aldehyde dipolarophiles

dipolarophile / substrate	p-MeO-Ph—CHO	Ph—CHO
3	16% (29)	7% (30)

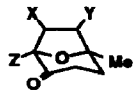
Products



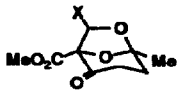
18 (X=EtO, Y=H, Z=H)
19 (X=H, Y=CO_2Me, Z=H)
20 (X=CO_2Me, Y=H, Z=H)
21 (X=H, Y=CO_2Me, Z=CO_2Me)



28 (X=BzlO)



22 (X=TMSO, Y=H, Z=H)
23 (X=BzlO, Y=H, Z=H)
24 (X=AcO, Y=H, Z=H)
25 (X=CO_2Me, Y=H, Z=H)
26 (X=H, Y=CO_2Me, Z=H)
27 (X=BzlO, Y=H, Z=CO_2Me)



29 (X=p-MeO-Ph)
30 (X=Ph)

Mechanistic studies by Houk,[9a,b] Huisgen,[9c,d] and Sustmann[9e] suggest that the order of reactivity might be explained using frontier molecular orbitals. According to Houk's qualitative analysis, electron withdrawing groups connected to the dipole or dipolarophile will lower both HOMO and LUMO energy levels, whereas donating groups will raise HOMO and LUMO levels. So that the cases with diazoketone **16** tend to be HOMO (of the dipole)-controlled reactions, and the ones with diazoketoester **3** tend to be LUMO-controlled reactions.[9f]

The dipolarophiles newly introduced in this report, such as ethoxyacetylene **7**, vinyloxytrialkylsilanes (**8**, **9**, **10**) and benzylvinylether **17** would be synthetically quite useful since they furnish oxygen functional group(s) on to the newly formed carbocyclic bridgehead. Ethylvinylether and vinylacetate have been previously reported to serve this purpose. However, ethylvinylether would require harsh conditions to cleave the ether bond after cycloaddition. Vinylacetate seems to work well with relatively electron-rich carbonyl ylides, but not with electron-deficient carbonyl

ylide such as the ones from 3 and 14. Considering there have not been many electron-rich dipolarophiles reported in this cyclization-cycloaddition reaction, these dipolarophiles would complement the existing dipolarophiles and expand the scope of this reaction.

Acknowledgment is most gratefully made to Dr. Byron Arison for NOE measurements and helpful discussions.

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6. The structures of the cycloadducts were fully characterized by ^{1}H-, ^{13}C-NMR and DEPT spectra. **5**: ^{1}H-NMR(400MHz, $CDCl_3$) δ1.41(3H, s), 2.00(1H, ddd, J=1.3Hz, 8.6Hz, 13.4Hz), 2.21(1H, ddd, J=1.1Hz, 7.3Hz, 13.4Hz), 2.32(1H, ddd, J=1.5Hz, 10.0Hz, 13.4Hz), 2.49(1H, ddd, J=1.3Hz, 7.3Hz, 17.0Hz), 2.83(1H, m), 3.79(1H, s), 4.76(1H, dd, J=3.2Hz, 10.0Hz). ^{13}C-NMR(100MHz, $CDCl_3$): -0.19, 26.32, 34.92, 37.72, 45.29, 52.47, 75.15, 81.55, 91.93, 167.88, 200.30. Anal. Calcd for $C_{13}H_{22}O_5Si$: C 54.52 H 7.74 Found: C 54.68 H 7.56. FT-IR (film): 2954.4, 1752.7, 1730.7. NOE was observed between C1-methyl group and C7-α hydrogen which is cis to C6-hydrogen by J=10Hz.
7. **5** was successively treated with a) $NH_2OH \cdot HCl$, Py b) TBAF, THF to give **11**. **11** was recrystalized from ethylacetate (mp 190°C). Crystal structure details: $C_{10}H_{15}NO_5$, M_r = 229.23, monoclinic, $P2_1/c$, a = 7.9494(9), b = 11.076(2), c = 12.551(3) Å, β = 97.56(1)°, V = 1095.5 Å^3, Z = 4, D_x = 1.390 g cm^{-3}, monochromatized radiation $\lambda(K_\alpha)$ = 1.541838 Å, μ =0.91 mm^{-1}, $F(000)$ = 488, T = 294 K. Data collected on a Rigaku AFC5 diffactometer to a θ limit of 71° with 1258 observed, at $I \geq 3\sigma(I)$, reflections out of 2305 measured. Structure solved by direct methods (SHELXS, G.M. Sheldrick, *Acta Crystallogr.*, 1990, A46, 467-473) and refined using full-matrix least-squares on F using 145 parameters. All non-hydrogen atoms refined with anisotropic thermal displacements. Final agreement statistics are: R = 0.047, wR = 0.046, S = 1.84, $(\Delta/\sigma)_{max} < 0.01$. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in final difference Fourier map is 0.21(4) eÅ^{-3} with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
8. Ethoxyacetylene was purchased from Aldrich Chemical Co., Inc. Vinyloxytrimethylsilane **8** was purchased from Huls America Inc. Vinyloxy-t-butyldimethylsilane **10** was prepared following the procedure of Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, *43*, 3791. (Z)-1,2-bis-trimethylsiloxyethene **9** was prepared by the procedure of Scharf H.-D., Mattay, J. *Tetrahedron Lett.* **1976**, *39*, 3509.
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(*Received in USA* 21 *June* 1994; *revised* 7 *October* 1994; *accepted* 14 *October* 1994)