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# Template-Directed C–H Insertion: Synthesis of the Dioxabicyclo[3.2.1]octane Core of the Zaragozic Acids

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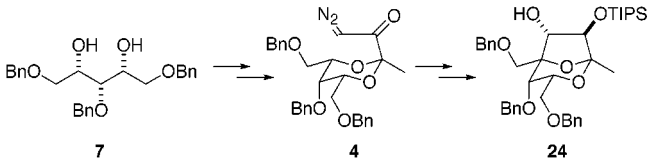
## ABSTRACT




**The preparation of (±)-24, a model for the core of the zaragozic acids, is reported. The pivotal reaction in this endeavor is the dirhodium(II)-catalyzed intramolecular C–H bond insertion of 2-diazoacetyl-1,3-dioxane 4, a transformation which generates four of the six stereocenters present in the core structure. A novel method for the diastereoselective synthesis of pyruvic acid acetals was also developed and employed in the preparation of 4 from xylitol derivative 7.**

During the past two decades, the dirhodium(II)-catalyzed decomposition of α-diazocarbonyl compounds and intramolecular C−H insertion of the resulting Rh carbenoids has emerged as a particularly powerful methodology for the construction of carbocyclic and heterocyclic rings.[1] Herein we report a method for the preparation of 2,8-dioxabicyclo-[3.2.1]octanones involving the C−H insertion of 2-diazoacetyl-1,3-dioxanes. We also report the application of this insertion strategy to the synthesis of the acetal core of the zaragozic acids (squalestatins). This family of fungal metabolites, first isolated in 1992 by groups at Merck[2] and Glaxo,[3] respectively, share a common 2,8-dioxabicyclo[3.2.1]-octane-3,4,5-tricarboxylic acid core which houses an array of six contiguous stereocenters. Since the zaragozic acids are potent inhibitors of mammalian squalene synthase, the enzyme responsible for the first committed step of cholesterol biosynthesis, they are potential therapeutic agents for the treatment of hypercholesterolaemia.[2]

The unique structure and potent biological activities associated with the zaragozic acids have, not surprisingly, stimulated intense synthetic interest.[4,5] A widely used strategy has been the preparation and acetalization of highly functionalized ketone polyols which contain up to five of the six stereocenters present in the natural product. Unfortunately, this bicyclization strategy has, in some cases, been compli-

(1) Reviews: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998. (b) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797−1815. (c) Taber, D. F. *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21a, pp 1127−1148. (d) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091−1160. (e) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145−3169.

(2) For a review of the discovery, biosynthesis, and mechanism of action of the zaragozic acids, see: Bergstrom, J. D.; Dufresne, C.; Bills, G. F.; Nallinomstead, M.; Byrne, K. *Annu. Rev. Microbiol.* **1995**, *49*, 607−639 and references therein.

(3) Baxter, A.; Fitzgerald, B. J.; Hutson, J. L.; McCarthy, A. D.; Motteram, J. M.; Ross, B. C.; Sapra, M.; Snowden, M. A.; Watson, N. S.; Williams, R. J.; Wright, C. *J. Biol. Chem.* **1992**, *267*, 11705−11708.

(4) Review: Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622−1656.

(5) For a review of work not covered in ref 4, see: Armstrong, A.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020−7032 and references therein.

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cated by formation of isomeric bicyclic acetals.[4,5] Intrigued by the pseudo $C_2$-symmetrical nature of the acetal core of **1** (Figure 1), we believed that a synthetic strategy centered

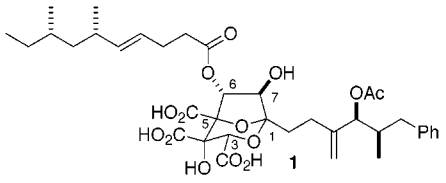
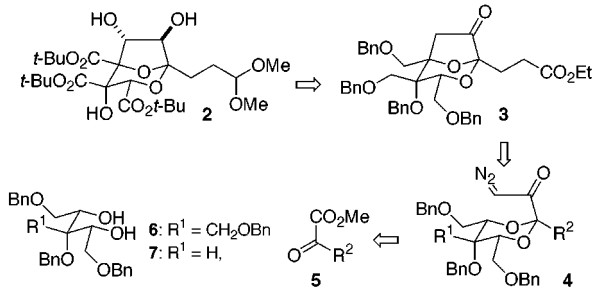


**Figure 1.**

upon formation of the 5/6 C−C bond would enable us to set four of the six asymmetric centers within the acetal core in a single transformation since this disconnection would generate a *meso* precursor.[6] The retrosynthetic disconnections which form the basis of this planned synthesis of zaragozic acid A (**1**) are illustrated in Scheme 1.

**Scheme 1.** Retrosynthetic Analysis



Removal of the C-6 *O*-acyl side chain and disconnection at C-3/4′ of **1** (Figure 1) leads to **2** which is the relay compound in Heathcock's synthesis of **1**.[7] Further disconnection of **2** generates **3** which could be obtained from **4** by transannular C−H insertion. From this point, the synthetic problem is now reduced to an exercise in the stereocontrolled preparation of a symmetrical 1,3-dioxane. Under thermodynamically controlled conditions, acetalization of **6** or **7** with pyruvate derivative **5** should favor the diastereomer in which the C-2 carboxylate group adopts the axial position.[8] While the synthesis of **1** will require us to prepare **6** and address the introduction of a C-1 side chain other than methyl, our initial studies have been directed toward the preparation of **24** (Scheme 3) from xylitol derivative **7** and methyl pyruvate **5** ($R^2$ = Me).

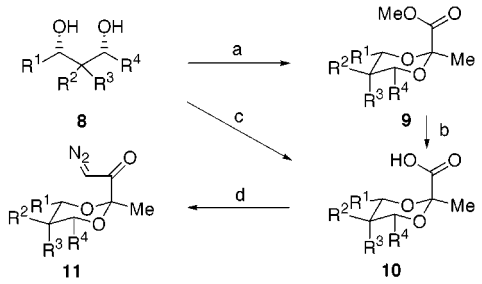
(6) While this work was in progress, Wills and co-workers reported a related approach to the zaragozic acids based on alkylidene carbene insertion: Walker, L. F.; Connolly, S.; Wills, M. *Tetrahedron Lett.* **1998**, *39*, 5273−5276.

(7) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115−9125.

(8) 2-Carboxy-1,3-dioxanes display a pronounced preference (~4 kcal/mol) for the axially oriented 2-carboxylate group: Bailey, W. F.; Eliel, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 1798−1806.

Before embarking on the synthesis of **24**, our investigation began with the preparation of a range of simple 2-diazoacetyl-1,3-dioxanes **11**. Following a protocol reported by Ziegler,[9] treatment of a solution of **8a**−**d** (Table 1, entries

**Table 1.** Preparation 2-Diazoacetyl-1,3-dioxanes **11**[a]



| entry | **8** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | method[a] | **11** | yield (%)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **8a** | H | Me | Me | H | a, b, d | **11a** | 61 |
| 2 | **8b** | H | Et | Et | H | a, b, d | **11b** | 60 |
| 3 | **8c** | H | $(CH_2)_4$ | | H | a, b, d | **11c** | 68 |
| 4 | **8d** | Me | H | H | Me | a, b, d | **11d** | 80 |
| 5 | **8e** | H | H | H | H | c, d | **11e** | 49 |

[a] Methods: (a) $MeCOCO_2Me$, $BF_3{\cdot}Et_2O$, $CH_3CN$, rt, 16 h; (b) NaOH, THF, $H_2O$, reflux, 5 h; (c) (i) $MeCOCO_2H$, Amberlite IR-120, PhH, reflux 16 h; (ii) NaOH, $H_2O$, reflux, 2 h. (d) (i) $Et_3N$, $CH_2Cl_2$, −20 °C; (ii) *i*-BuOCOCl, −20 °C, 5 min; (iii) $CH_2N_2$, $Et_2O$, −20 °C → rt, 16 h. [b] Overall yield of **11** from **8** after purification by flash chromatography.

1−4) in acetonitrile with $BF_3{\cdot}Et_2O$ (2 equiv) and methyl pyruvate (2 equiv) gave **9** which were then saponified to furnish the corresponding carboxylic acids **10**. On the other hand, substrate **10e** (entry 5) was prepared by acid-catalyzed acetalization of 1,3-propanediol (**8e**) (1.5 equiv) and pyruvic acid (1.0 equiv) followed by saponification of the resulting mixture of ester products.[10] Encouragingly, in the case of **8d** (entry 4), acetalization provided a single diastereomer in which the C-2 carboxylate group was found to be in the axial orientation, trans to the equatorial ring substituents. The relative configuration of the acetal stereocenter in this case was determined using $^{13}C$ NMR spectroscopy, examining the C-2 methyl group ($\delta$ 26.8 ppm) which is known to be sensitive to the relative configuration of the adjoining acetal.[11]

Treatment of **10** with $Et_3N$ and isobutyl chloroformate now generated the corresponding mixed anhydrides which, upon treatment with an ethereal solution of diazomethane, provided the α-diazo ketones **11** in good yield.[12] With a protocol for the preparation of **11** established, attention now turned to the C−H insertion. Thus, slow addition of **11a** to dirhodium(II) tetraacetate ($Rh_2(O_2CCH_3)_4$) (2 mol %) in $CH_2Cl_2$ afforded **12a**, the product of transannular C−H insertion, in 52% yield together with a small amount of **13a (**4%) (Table 2, entry 1). This bicyclic enol ether proved to be rather

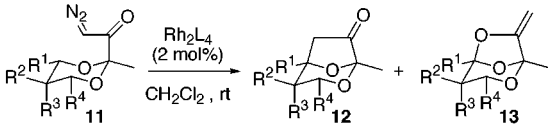
(9) Ziegler, T. *Tetrahedron Lett.* **1994**, *35*, 6857−6860.

(10) Newman, M. S.; Chen, C. C. *J. Org. Chem.* **1973**, *38*, 1173−1177.

(11) Gorin, P. A. J.; Mazurek, M.; Iacomini, M.; Duarte, J. H. *Carbohydr. Res.* **1982**, *100*, 1−15.

(12) Plucinska, K.; Liberek, B. *Tetrahedron* **1987**, *43*, 3509−3517.

**Table 2.** Preparation of 2,8-Dioxabicyclo[3.2.1]octanones **12**[a]



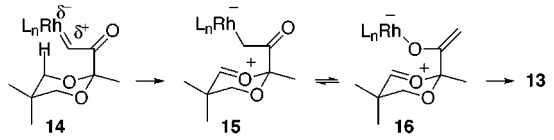

| entry | 11 | method[a] | yield (%) of **12**[b] | yield (%) of **13**[b] |
|---|---|---|---|---|
| 1 | **11a** | a | 52 | 4 |
| 2 | **11a** | b | 45 | 5 |
| 3 | **11b** | a | 42 | 12 |
| 4 | **11c** | a | 50 | 11 |
| 5 | **11d** | a | 50 | |
| 6 | **11e** | a | 44 | |

[a] Methods: (a) a solution of **11** in $CH_2Cl_2$ was added via syringe pump to a solution of $Rh_2(O_2CCH_3)_4$ (2 mol %) in $CH_2Cl_2$ (0.023 M), over 20 h; (b) a solution of **11** in $CH_2Cl_2$ was added via syringe pump to a solution of $Rh_2(cap)_4$ (2 mol %) in $CH_2Cl_2$, at reflux, over 72 h. [b] Yields of **12** and **13** after purification by flash chromatography.

unstable to silica gel chromatography in addition to being volatile. Cyclization of substrates **12b**−**e** (entries 3−6) under these conditions provided similar yields of **12**, while **13** was isolated from the reactions of **11b** and **11c** only.

With regard to the formation of **13**, Clark and co-workers recently reported the formation of analogous products during the diazo decomposition of α-diazo-α′-alkoxy ketones.[13] According to Clark's mechanistic rationale, the rhodium carbenoid species generated upon diazo decomposition of **11a** faces two possible fates: (i) concerted C−H insertion to form **12a** or (ii) oxygen-assisted hydride transfer to the electron-deficient carbene center, generating oxonium ion−rhodium enolate species **15**. Cyclization of **15**, or its enol tautomer **16**, could then generate **12a** or **13a** (Scheme 2).

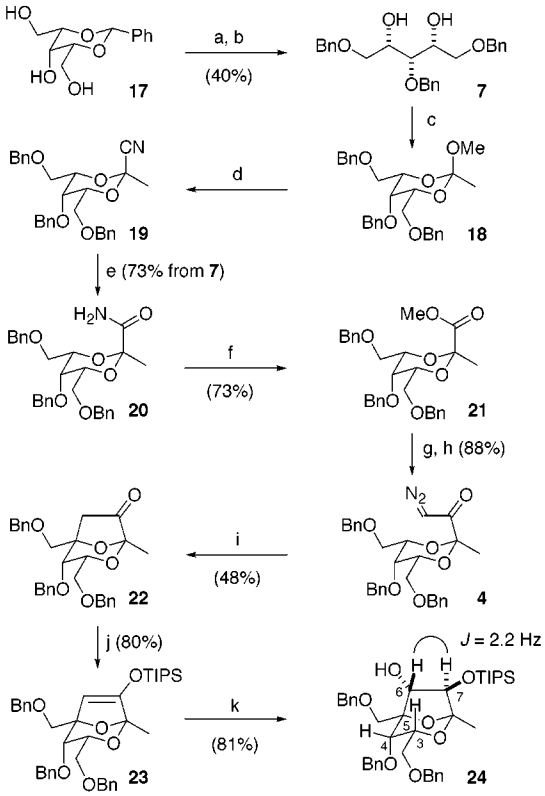
**Scheme 2**




Hydride transfers have also been reported by Doyle and White,[13b,c] who note that this process becomes prevalent when the oxonium ion species **15**/**16** are stabilized. Reasoning that a less electrophilic catalyst might suppress hydride transfer and favor insertion, dirhodium(II) tetra(caprolactamate) ($Rh_2(cap)_4$) was examined as a catalyst. However, decomposition of **11a** was prohibitively slow at room temperature and only proceeded upon heating for 72 h. The yields of **12a** and **13a** in this case were similar to those found with $Rh_2(O_2CCH_3)_4$ (entry 2). It appears that bis-α-alkoxy-α′-diazoketones **11** are more resistant to diazo decomposition than other α-diazo ketones and may be due to the electron-withdrawing effect of the acetal group adjoining the diazo center.[1a]

Our synthesis of the zaragozic acetal core itself commenced from 3,5-*O*-benzylidene xylitol (**17**)[14] which was *O*-alkylated (NaH, BnBr, DMF) to provide the corresponding tribenzyl ether in 51% yield (Scheme 3). Removal of the benzylidene acetal proceeded smoothly to provide **7** upon treatment with ethanethiol and a catalytic amount of *p*-TsOH in chloroform. With the precedent gained in our initial study, it was now anticipated that acetalization of **7** with methyl pyruvate would provide 1,3-dioxane **21**. All attempts to effect this transformation using Ziegler's protocol, however, resulted in the decomposition of **7**. In view of the centrality of this transformation to our synthesis, it was decided to

**Scheme 3.** Synthesis of the Zaragozic Core Acetal **24**[a]




[a] Reagents and conditions: (a) NaH, BnBr, $Bu_4NI$, DMF, rt, 20 h; (b) EtSH, *p*-TsOH, $CHCl_3$, rt, 48 h; (c) (i) $MeC(OMe)_3$, *p*-TsOH, 4 Å molecular sieves, $CH_2Cl_2$, rt, 30 min; (ii) $Na_2CO_3$; (d) $Me_3SiCN$, $SnCl_2$, 4 Å molecular sieves, $CH_2Cl_2$, reflux, 1.5 h; (iii) $K_2CO_3$; (e) NaOH, $H_2O_2$, EtOH, reflux, 1 h; (f) DMF-DMA (3.5 equiv), MeOH, 100 °C, 72 h; (g) LiOH, THF, $H_2O$, 4 h, reflux; (h) (i) $Et_3N$, rt, 30 min; (ii) *i*-BuOCOCl, $CH_2Cl_2$, −30 °C, 30 min; (iii) $CH_2N_2$, 0 °C, 1 h; (i) $Rh_2(OAc)_4$, $CH_2Cl_2$, rt, 8 h; (j) (i) KHMDS, THF, −78 °C, 40 min; (ii) TIPSCl, −78 °C, 30 min; (k) (i) $BH_3$·$Me_2S$, THF, reflux, 5 h; (ii) $H_2O_2$, 0.6 M NaOH, rt, 48 h.

(13) (a) Clark, J. S.; Dossetter, A. G.; Russel, C. A.; Whittingham, W. G. *J. Org. Chem.* **1997**, *62*, 4910−4911. (b) Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619−621. (c) White, J. D.; Hrnciar, P. *J. Org. Chem.* **1999**, *64*, 7271−7223.

(14) Hann, R. M.; Ness, A. T.; Hudson, C. S. *J. Am. Chem. Soc.* **1946**, *68*, 1769−1774.

develop an alternative pyruvate acetal synthesis which would be compatible with the labile *O*-benzyl protecting groups. To this end, ortho ester **18** was prepared as a single isomer by treating **7** with trimethyl orthoacetate in the presence of a catalytic amount of *p*-TsOH.[15] The relative stereochemistry of **18** was established by examination of the NOESY spectrum which showed correlations between the axially positioned C-2 methoxyl group and the adjacent C-4/6 hydrogens. Since **18** proved to be susceptible to hydrolysis, it was immediately treated with trimethylsilyl cyanide ($Me_3SiCN$) and $SnCl_2$ in $CH_2Cl_2$.[16] Upon heating to reflux for 1.5 h, cyanation proceeded to give **19** as a single isomer in high yield.[17] Hydrolysis of this material with alkaline hydrogen peroxide then gave **20** in 73% overall yield from **7**. Following a method recently reported by Brocchetta,[18] **20** was now converted to the corresponding methyl ester **21** in 73% yield by heating with dimethylformamide dimethyl acetal (DMF-DMA) in methanol at 90 °C (sealed tube) for 72 h.

With **21** secured, α-diazo ketone **4** was now prepared in 88% yield by a sequence of saponification, mixed anhydride formation, and in situ treatment with diazomethane. Upon slow addition of **4** to a solution of $Rh_2(OAc)_4$ (2 mol %) in $CH_2Cl_2$ at room temperature, diazo decomposition proceeded smoothly to afford **22** in 49% yield. Prompted by a report from Brown[19] describing the regioselective hydroboration of 3-methoxy-2,5-dihydrofuran, we now decided to investigate the hydroboration of **23** as means of installing the C-6/7 *trans* diol moiety in a single operation. Deprotonation of **22** with KHMDS in THF and addition of TIPSCl furnished **23** which smoothly underwent hydroboration ($BH_3 \cdot Me_2S$) in THF upon heating at reflux for 5 h. Oxidation of the resulting borane with alkaline hydrogen peroxide proved to be rather slow, taking 48 h to reach completion, but ultimately provided the differentially protected diol **24** in 81%. The relative stereochemistry of **24** was confirmed by measurement of scalar couplings and NOESY correlations: H-7 ($\delta$ 4.06 ppm) appeared as a doublet ($J = 2.2$ Hz) while H-6 ($\delta$ 4.00 ppm), a multiplet, displayed NOESY correlations to H-3 ($\delta$ 4.38 ppm) and H-4 ($\delta$ 3.50 ppm). The 2.2 Hz coupling constant between the C-6 and C-7 hydrogens is diagnostic of their *anti* relationship[5] and confirms that hydroboration proceeded from the *exo* face of **23**.

In summary, the acetal core of the zaragozic acids **24** has been prepared in 11 steps from **17** using a C−H bond insertion strategy which sets four of the six stereocenters of the natural product. Investigations of the asymmetric desymmetrization of **4** and installation of the C-1 side chain present in **1** are now in progress and will be reported in due course.

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**Supporting Information Available:** Full experimental procedures and spectral data for compounds **4**, **7**, **9**−**13**, and **17**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0158361

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(16) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967−973.
(17) Axially orientated 2-methoxy-1,3-dioxanes are known to undergo nucleophilic substitution with retention at C-2: (a) Eliel, E. L.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 584−590. (b) Rychnovsky, S. D.; Kim, J. *Tetrahedron Lett.* **1991**, *32*, 7223−7224.
(18) Anelli, P. L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* **1997**, *38*, 2367−2368.
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