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Diastereoselective Acetylide Additions to a [3.2.1]–Dioxabicyclooctanone: Installation of the C(4) Stereocenter of (+)-Zaragozic Acid C

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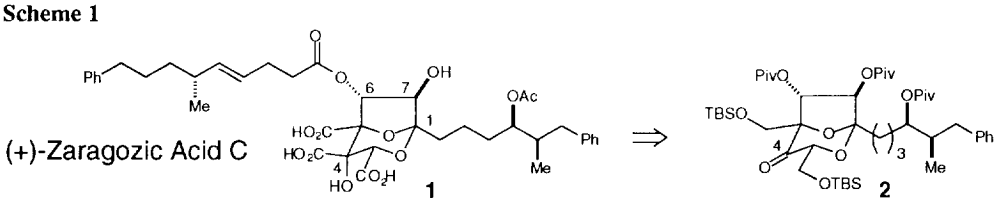
Abstract: Nucleophilic addition of lithium acetylides to ketone **2** provides a key intermediate in the synthesis of (+)–zaragozic acid C. The effect of co–solvents (tertiary amines) and additives (LiBr) on the diastereoselection of this reaction has been investigated.

The zaragozic acids and squalestatins constitute a family of structurally related fungal metabolites that are potent picomolar inhibitors of squalene synthase.[1] These natural products share a densely functionalized [3.2.1]–dioxabicyclooctane core and differ exclusively at the C(1) and C(6) alkyl and *O*–acyl appendages, respectively. We have recently described a synthesis of (+)-zaragozic acid C **1** in which ketone **2** is a key intermediate (Scheme 1).[2,3,4] In the course of our studies, we have observed unexpected diastereoselection in nucleophilic additions of lithium acetylides to this bicyclic ketone in Et_2O–tertiary amine solvent systems. Experimental conditions were found which resulted in preferential formation of the desired C(4)–epimer, the result of addition to the nominally more hindered face of the ketone. This letter provides an account of these observations.

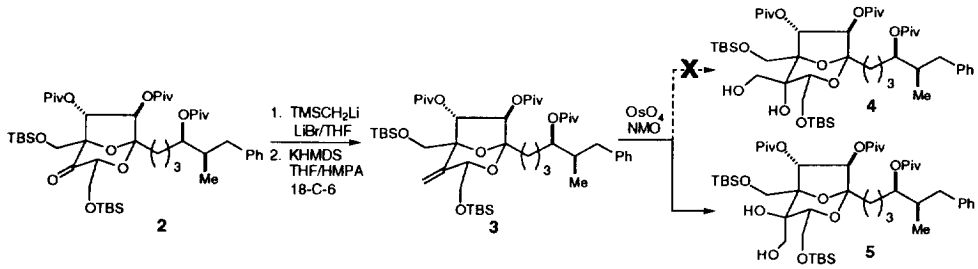
Scheme 1



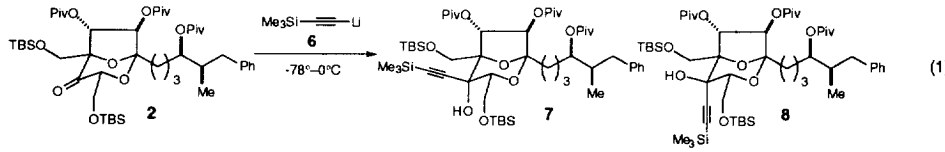
In principle, there are two general strategies by which the carbinol stereocenter at C(4) can be installed: (1) oxidative functionalization of alkene **3**; and (2) nucleophilic addition to ketone **2**. ^1H NMR NOE difference experiments suggest that both ketone **2** and the derived alkene **3** are found with the dioxane ring in the chair conformation as shown. Thus, on the basis of molecular models, we anticipated that dihydroxylation of dioxabicyclooctane **3** would occur preferentially from the convex face to provide the desired C(4) carbinol **4**. Conversely, generation of the same C(4) carbinol would require nucleophilic attack of ketone **2** from the concave face. Therefore, we initially examined dihydroxylation of **3** (Scheme 2). Methenylation of **2** was successfully accomplished through a two-step Peterson olefination sequence under carefully controlled reaction conditions. Unexpectedly, when

2 was treated with catalytic OsO_4 (acetone/H_2O, NMO) a single diol diastereomer **5** possessing the undesired stereochemistry at C(4) was isolated. This as well as additional results led us to reevaluate our synthetic plan.[5]

Scheme 2



We then proceeded to examine nucleophilic additions of carboxylate equivalents to **2**. Addition of ketone **2** to a solution of lithium acetylide **6** in THF gave a mixture of carbinol products in 95% yield (Eq 1).[6] Following alkyne desilylation, the diastereomeric mixture could be readily separated by chromatography on silica gel. ^{1}H NMR NOE analysis revealed that the addition had occurred with a slight preference from the concave face of the C(4) ketone giving a 1.5:1 mixture of **7**:**8** (Table 1, Entry 1). When **2** was added to a THF/TMEDA solution of acetylide **6** the stereoselectivity reversed, and a 1:2 mixture of propargyl alcohol diastereomers **7**:**8** was isolated (Entry 2).



(1)

The use of Et_2O as solvent had a beneficial effect on the reaction diastereoselection (Entry 7, **7**:**8** = 3.5:1). Additionally, the product distribution could be significantly altered through the use of either co-solvents or additives. A solvent mixture consisting of 1:1 diglyme/Et_2O led to a decrease in the ratio of **7**:**8** (Entry 4). When the reaction was conducted with 1 equiv of LiBr the diastereoselectivity was attenuated slightly (Entry 6); in contrast, the presence of excess LiBr led to a reversal in the stereochemical outcome, favoring the formation of the unwanted C(4) epimer **8** (Entry 3). The above results suggested that the reaction diastereoselection might be influenced by changes to the aggregation state of the lithium acetylide.[7] Solution studies of lithium acetylides indicate that their aggregation equilibria may be altered in the presence of added tertiary amines (*vide infra*). On this basis, we investigated the effect of amine co-solvents on the reaction diastereoselection.[8] The use of Et_2O–tertiary amine solvent combinations led to dramatic improvements in the product ratio of **7**:**8** (> 3.5:1, Entries 8,9,10). The most pronounced increase was observed with a 1:1 Et_2O-Me_3N solvent mixture, which furnished a 6.1:1 mixture of **7**:**8**.[9]

Table 1. Nucleophilic additions of acetylide **6** to ketone **2**

Entry	Conditions[a]	Diastereoselectivity 7:8[b]
1	THF	1.5 : 1
2	THF/TMEDA	1 : 2
3	Et_2O/150 equiv LiBr	1 : 1.7
4	Et_2O/diglyme	2.2 : 1
5	Et_2O/py	2.1 : 1
6	Et_2O/1 equiv LiBr	3.1 : 1
7	Et_2O	3.5 : 1
8	Et_2O/*i*-Pr_2NEt	3.8 : 1
9	Et_2O/Et_3N	4.3 : 1
10	Et_2O/Me_3N	6.1 : 1

(a) Reactions were conducted at -78 °C with slow warming to 0 °C in a 1:1 mixture of co-solvents with the exception of Entry 5 (3:1 Et_2O–Py) ; (b) The diastereoselectivity was determined by integration of the ^1H NMR C(6) methine resonances for **7** and **8** at δ 5.51 and 5.72 ppm, respectively.

The structure of lithium acetylides has been studied in the solid-state and in solution. The X-ray crystal structure of PhC≡C–Li reveals a dimer with bridging phenylethynyl units between the Li^+ cations.[10] In solution, PhC≡C–Li has been reported to exist as an equilibrating mixture of dimeric and tetrameric forms.[11] This has been elegantly demonstrated using cryoscopic and NMR techniques. Fraenkel has investigated the effect of solvent and amine additives on the $[Me_3CC{\equiv}C–Li{\bullet}(THF)_x]_2 \rightleftarrows [Me_3CC{\equiv}C–Li{\bullet}(THF)_y]_4$ equilibrium using ^6Li and ^{13}C NMR spectroscopy.[12] In these studies, diamines such as TMEDA in THF favored the dimeric acetylide, whereas tetrameric aggregation states appeared to prevail when simple ethers (Et_2O) and tertiary amines were employed. In combination with these spectroscopic studies, our findings suggest that the observed reaction diastereoselection may be dependent on the aggregation state of the acetylide.

In conclusion, nucleophilic addition of **6** to [3.2.1]-dioxabicyclooctanone **2** leads optimally to the desired adduct **7**, a key intermediate in the synthesis of (+)-zaragozic acid C, when the reaction is conducted in Me_3N–Et_2O solvent. This tertiary carbinol is the product arising from addition to the nominally more hindered face of the octanone. The use of amine co-solvents should find applications in other diastereoselective carbonyl addition reactions.

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Footnotes and References

(1) (a) Zaragozic Acid C: Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizol, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221. (b) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261, and references therein. (c) Squalestatins: Dawson, M. J.; Farthing, J. E.; Marshall, P.S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiotics* **1992**, *45*, 639, and references therein.

(2) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *106*, 10825.

(3) Evans has also reported the total synthesis of zaragozic acid C, see: Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 0000.

(4) The synthesis of zaragozic acid A/Squalestatin S1 has been reported, see: Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S. *Angew. Chem,. Int. Ed. Engl.*, **1994**, *33*, 2190.

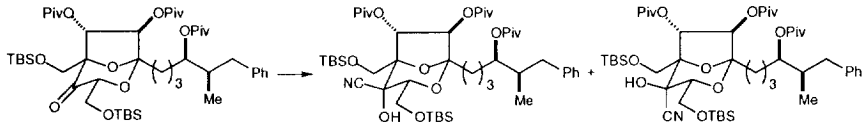
(5) Studies involving osmylation and epoxidation of **3** and its deprotected variants are beyond the scope of this letter and will be reported shortly.

(6) We have described the conversion of alkyne **7** to the corresponding C(4) carboxylate, see ref. 3.

(7) For an interesting discussion of the structure and reactivity of enolates related to aggregation phenomena, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(8) The effect of Et_3N and TMEDA in diastereoselective Grignard additions to chiral ketooxazolines has been documented, see: Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785.

(9) More recently, we have shown that **2** can be converted to either corresponding cyanohydrin diastereomer by reaction with HCN or TMSCN. Thus, it may be possible to utilize the cyanohydrin as a mask for the C(4) α-hydroxy carboxylic acid, and to prepare either the natural or C(4) epimer of zaragozic acid C. Details of this work will be reported in due course.



2

HCN (g)/toluene/0°C	1:3
TMSCN/cat. CsF	5:1

(10) (a) Schubert, B.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 496. (b) Schubert, B.; Weiss, E. *Chem. Ber.* **1983**, *116*, 3212. (c) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta.* **1983**, *66*, 308.

(11) Hässig, R.; Seebach, D. *Helv. Chim. Acta.* **1983**, *66*, 2269.

(12) Fraenkel, G. *Polym. Prepr., Am. Chem. Soc. Div. Polym. Chem.* **1986**, *27*, 132.

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