Pergamon

Tetrahedron Letters 40 (1999) 2691–2694

TETRAHEDRON LETTERS

An Approach to (+)-Pancratistatin from D-Glucose: A Conformational Lock Solves A Stereochemical Problem

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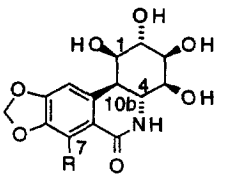
Received 13 January 1999; revised 4 February 1999; accepted 5 February 1999

Abstract

In previous work we discovered that reductive Pd-mediated aryl-enone cyclization of an advanced intermediate resulted in epimerization of a critical stereocenter. Analysis of conformational and steric effects could rationalize the result. Based on that analysis it was anticipated that a conformational lock could suppress the undesired epimerization. Results reported herein confirm that expectation.

Keywords: Arylation; Conformation; Cyclitols; Heck Reactions.

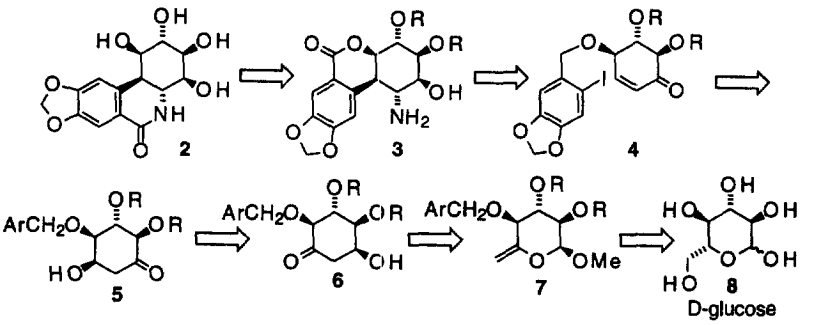
In 1984 the structure of (+)-pancratistatin (**1**) was reported, determined by NMR and X-ray crystallography, including the rigorous assignment of absolute configuration [3]. (+)-Pancratistatin has shown very promising anticancer activity [4,5,6].



1 (R = OH)
2 (R = H)

The first synthesis of pancratistatin, racemic **1**, was reported by Danishefsky and Lee in 1989 [7]. There are now 4 different total syntheses of (+)-pancratistatin; the 1995 synthesis by Hudlicky and coworkers [8], the 1995 synthesis by Trost and Pulley [9], the 1997 synthesis by Haseltine and coworkers [10], and the 1998 synthesis by Magnus and Sebhat [11]. In addition, several syntheses of 7-deoxypancratistatin (**2**) have been reported; by Paulsen and Stubbe [12], Keck and coworkers [13], Hudlicky and coworkers [14] and Chida and coworkers [15].

A few years ago we developed a synthetic strategy to prepare **1** in enantiomerically pure form starting from cheap and readily available D-glucose. The basic strategy is shown at right for 7-deoxypancratistatin (**2**). Notable features of our strategy include the utilization of the C1 β-oxo to deliver a tethered



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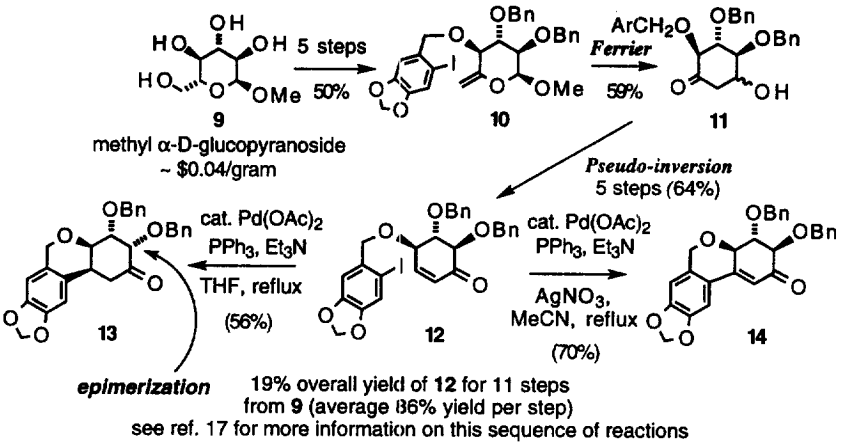
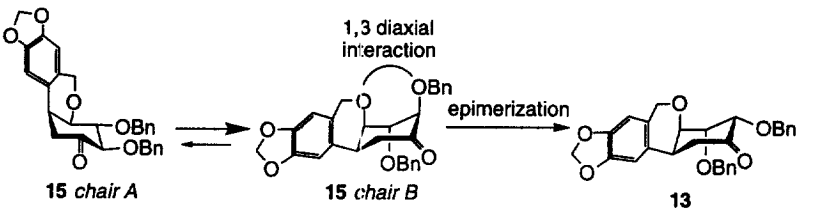
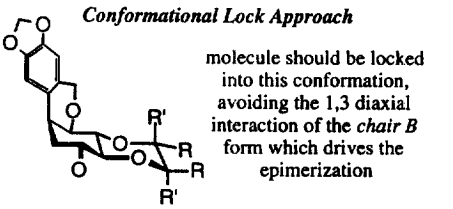
aryl group to the β face at C10b resulting in a cis-fused ring system, subsequent amination on the convex face and a lactone → lactam isomerization (**3** → **2**), a strategy employed in the Danishefsky/Lee synthesis of (±)-pancratistatin.



We discovered conditions to perform intramolecular Pd-catalyzed aryl-enone conjugate additions to produce either non-reductively cyclized compounds such as **14** or reductively cyclized compounds such as **13**. Model studies on these types of cyclizations were published [16] as well as an approach to the synthesis of 7-deoxypancratistatin (**2**) starting from methyl α-D-glucopyranoside (**9**) [17]. Methyl α-D-glucopyranoside (**9**) is easily prepared from D-glucose. The cyclization to form the reductively cyclized product **13** led to epimerization of the stereocenter alpha to the ketone as determined by an X-ray crystal structure of **13** [17].

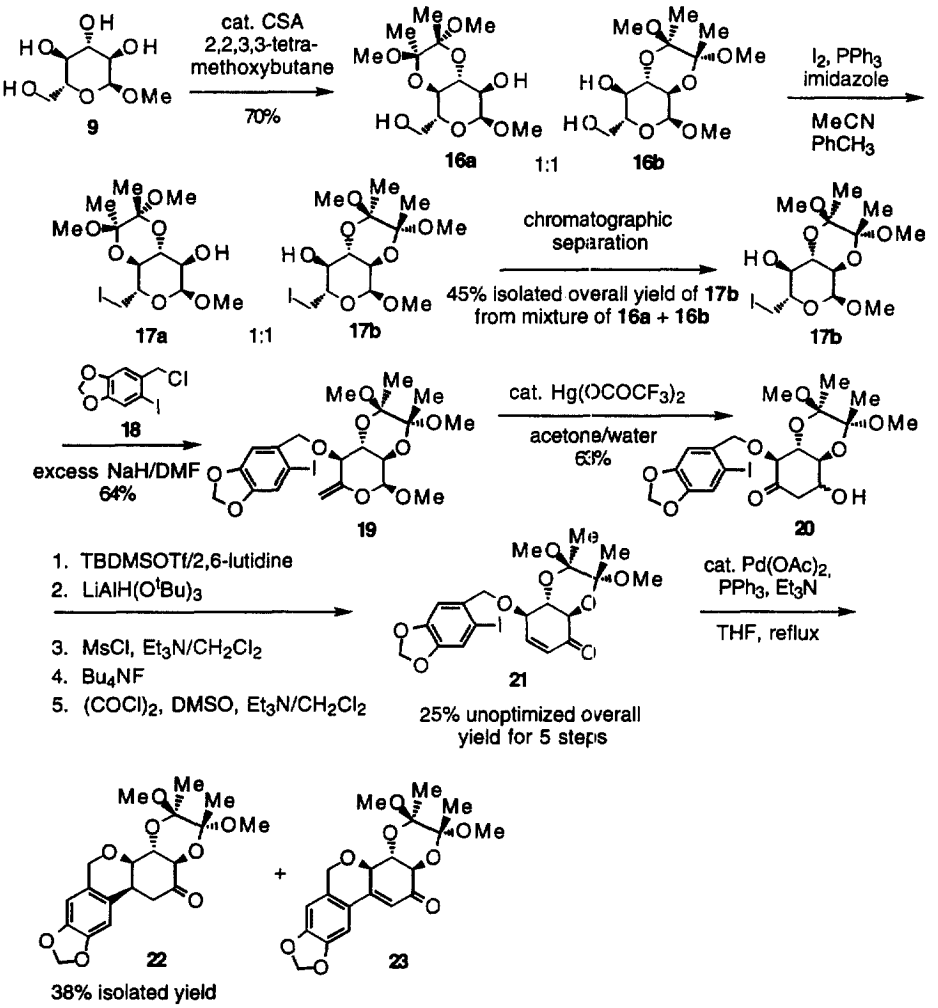


We hypothesized that the epimerization leading to the formation of **13** can be explained as shown at right. The conformation free energy difference (ΔG^0 or "A" value) between an axial phenyl group and an equatorial phenyl group is about 2.9 kcal/mole favoring equatorial phenyl [18]. The conformation free energy difference between an axial OR group and an equatorial OR group is much less and does not depend very much on the structure of R [18]. Using "A" values of 2.9 for phenyl and 0.7 for the three OR groups in **15** (an epimer of **13** and the presumed initial product of reductive cyclization), it is possible to estimate that the energy difference between **15** *chair A* and **15** *chair B* is 2.9 – 0.7 – 0.7 – 0.7 = 0.8 kcal/mole favoring **15** *chair B*. Epimerization of **15** *chair B* to **13** should result in a lowering of the energy by one OR "A" value, 0.7 kcal/mole, making **13** significantly lower in energy than **15**, shifting the equilibrium to provide **13** as the major product.



Based on the analysis of the epimerization reaction given above, it should be possible to avoid the epimerization by locking synthetic intermediates such as **15** into the **15** *chair A* conformation, thus avoiding the epimerization-promoting 1,3 diaxial interaction in **15** *chair B*. Ley's methods for reaction of a trans diequatorial 1,2-diol with 3,3',4,4'-tetrahydro-6,6'-spirobi-2H-pyran (bis-DHP) to give a dispiroacetal (Dispoke) or with 1,1,2,2-tetramethoxycyclohexane (TMC) to produce a cyclohexane 1,2-diacetal (CDA) could provide the necessary conformation lock [19]. A less expensive functionally equivalent alternative developed by Frost and coworkers is the butane 2,3-bisacetal group [20]. We decided to use the butane 2,3-bisacetal group as a conformational lock.

Treatment of α-methyl-D-glucopyranoside (**9**) with catalytic camphorsulfonic acid and 2,2,3,3-tetramethoxybutane in methanol provided **16a** and **16b** as a 1:1 mixture in 70% unoptimized yield [21]. That mixture could not be separated easily by chromatography so the mixture of **16a** and **16b** was converted to a 1:1 mixture of **17a** and **17b** using I_2:PPh_3:imidazole in acetonitrile/toluene. It was possible to separate **17a** and **17b** by chromatography, providing pure **17b** in 45% isolated unoptimized yield from **16a** + **16b** (90% from **16b**). The structure of **17a** was determined unambiguously by X-ray crystallography [22], thus providing a secure assignment of the structure of **17b** as shown. Alkylation of **17b** with **18**, with concomitant elimination of HI, produced **19** in 64% unoptimized yield. Ferrier rearrangement of **19** produced **20** in 63% unoptimized yield. The five-step "pseudoinversion" sequence of reactions shown [17] produced **21** in 25% unoptimized yield from **20**. Pd-catalyzed cyclization of **21** under conditions which should favor reductive cyclization (**22**) led to a mixture of **22** (reductive cyclization) and **23** (standard Heck non-reductive cyclization). Chromatographically purified **22** (38% isolated yield) produced diffraction quality crystals. X-ray crystallographic analysis of **22** showed that the structure of **22** is the non-epimerized structure shown below [22]. *This result demonstrates that the conformational lock served its intended purpose, to suppress epimerization in the reductive cyclization to convert **21** to **22**.*



Several possible ways can be envisioned to complete the synthesis of 7-deoxypancratistatin (**2**) from **22**. An attractive route involves the following key steps: electrophilic amination of the kinetic enolate of **22** from the convex face, benzylic oxidation to produce a lactone and a lactone → lactam isomerization. An analogous strategy could be used to produce (+)-pancratistatin (**1**).

Acknowledgment. This research was supported by NSF CHE-9423782, the Medical Research Foundation of Oregon and the Elsa U. Pardee Foundation for Cancer Research. The authors gratefully acknowledge Dr. Timothy Weakley for X-ray crystallographic determination of the structures of **17a** and **22**.

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[21] All new compounds (**16** - **23**) were characterized by ^{1}H NMR, ^{13}C NMR, IR and high resolution (exact) MS. In addition, satisfactory C, H elemental microanalyses were obtained for **17b** and three intermediates in the conversion of **20** to **21**.
[22] X-ray crystallographic data for **17a** and **22** have been provided to Tetrahedron Letters for deposition at the Cambridge Crystallographic Data Centre.