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An Approach to Pancratistatin from *myo*-Inositol

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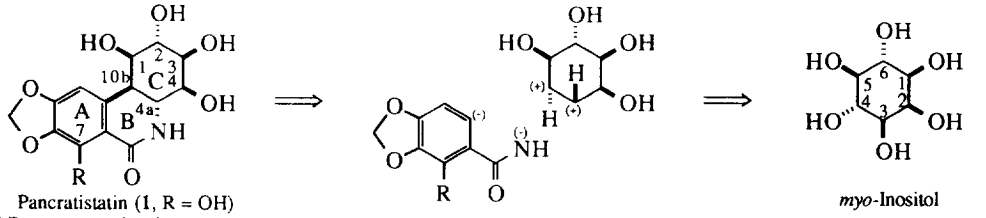
Abstract: A highly advanced intermediate (**15**) for the synthesis of 7-deoxypancratistatin was prepared in 11 steps from *myo*-inositol. Introduction of the C_{10b}-Ar bond through an intramolecular epoxide opening with an aryl anion is the key step in this approach.

Pancratistatin **1** is of interest because of its particularly promising anticancer activity, low natural abundance, and synthetically challenging structure which includes a cyclohexane ring with six stereocenters. Pettit and co-workers reported the isolation and activity of pancratistin in 1984,[3] but the low yield[4] of **1** from *Hymenocallis* (formerly *Pancratium*) *litoralis* (Jacq.) has precluded detailed study of its anticancer activity. A biosynthetic approach was recently reported by Pettit and co-workers[5] to obtain higher yields of **1** from cloned *Hymenocallis littoralis*. The homolog 7-deoxypancratistatin **2** was isolated by Ghosal and co-workers,[6] and has exhibited potent antiviral activity with a slightly improved therapeutic index relative to **1**.[7] The first synthesis of (±)-**1** was reported by Danishefsky group[8] in 1989 and recently, Hudlicky and co-workers[9] communicated a concise synthesis of (+)-**1**. Several syntheses of 7-deoxypancratistatin have been recorded,[10] including a very recent synthesis of (+)-**2** from D-gluconolactone by Keck and co-workers.[10c]

We envisioned that the stereochemical relationship between *myo*-inositol and the cyclohexane ring in **1** could be exploited (Scheme 1). Retrosynthetically, the disconnection of the aromatic amide dianion synthon leads to a *myo*-inositol synthon with inverted stereochemistry at the C_3 and C_4 hydroxyls (inositol numbering). In our approach, this stereochemical requirement is satisfied through sequential ring opening reactions of epoxides.

Scheme 1

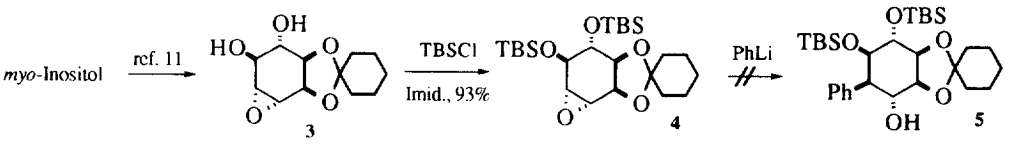


Pancratistatin (**1**, R = OH)
7-Deoxypancratistatin (**2**, R = H)

myo-Inositol

The ready availability of epoxide **4**, prepared by silylation of the known epoxy diol **3**,[11] led us to first explore C-C bond construction with simple phenyl organometallic reagents (Scheme 2).[12] Unfortunately, we could isolate none of the adduct **5** (nor its regioisomer) in several attempts under a variety of reaction conditions (e.g., PhLi or PhMgBr with and without $BF_3{\cdot}OEt_2$).

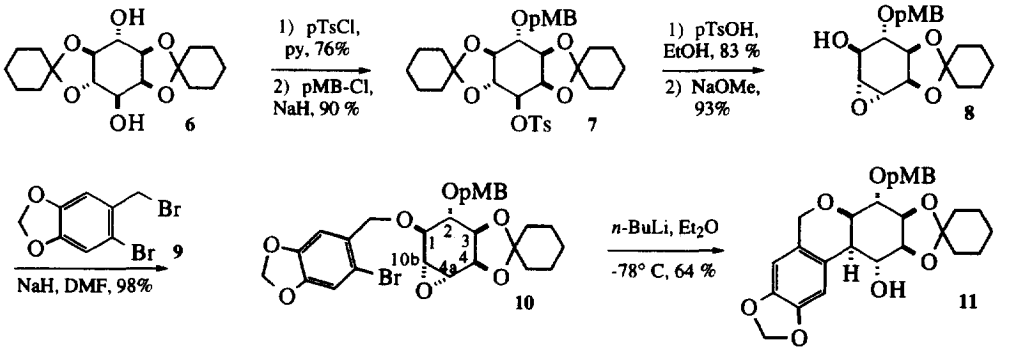
Scheme 2



3 **4** **5**

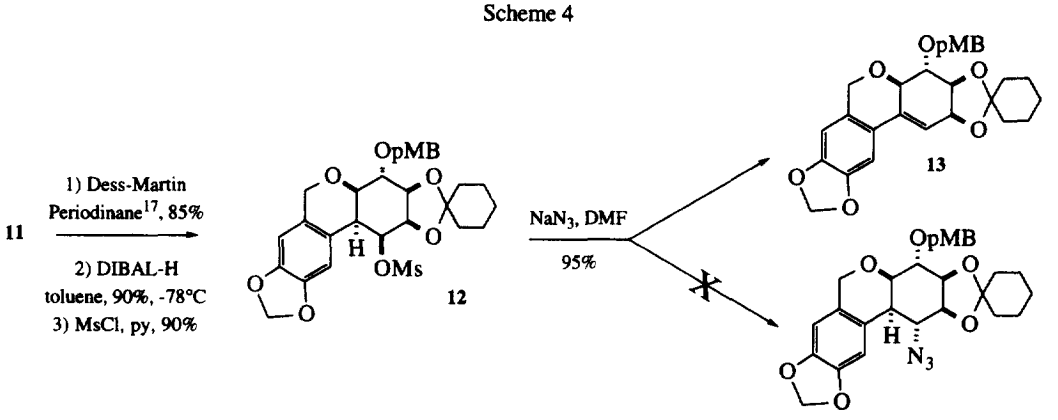
Speculating that the low reactivity of the epoxide **4** towards aryl organometallics could be overcome through the intramolecular delivery of the nucleophile,[13] we envisioned tethering the aryl organometallic moiety to the neighboring C_1 hydroxyl (pancratistatin numbering). In contrast to the previous intermolecular approach, this strategy required differentiation of the C-1 and C-2 hydroxyl functions. Towards this end, 1,2:4,5 bis-cyclohexylidene-inositol **6**[11d] was treated with *p*-toluenesulfonyl chloride, then *p*-methoxybenzyl chloride to give **7** (Scheme 3). The *trans*-cyclohexylidene ketal on **7** was selectively removed with *p*-TsOH and EtOH in CH_2Cl_2 and the resulting diol was refluxed with sodium methoxide in MeOH to give alcohol **8**. Because of the availability of 6-bromopiperonyl bromide **9**,[14] we first pursued 7-deoxypancratastatin **2** in order to establish the viability of the strategy. After tethering the latent aryl organometallic group to the C-1 hydroxyl of **8** under conventional conditions, we were delighted to find that treatment of **10** with *n*-BuLi resulted in rapid lithium-halogen exchange followed by a slower cyclization process to provide the desired product **11**[15] in 64% isolated yield.

Scheme 3



To introduce the requisite nitrogen functionality at C-4a, we initially explored the S_N2 displacement of the mesylate **12**, prepared from **11** by an oxidation-reduction sequence to give the inverted alcohol followed by mesylation (Scheme 4). Unfortunately, treatment of **12** with sodium azide cleanly produced the elimination product **13**.[16]

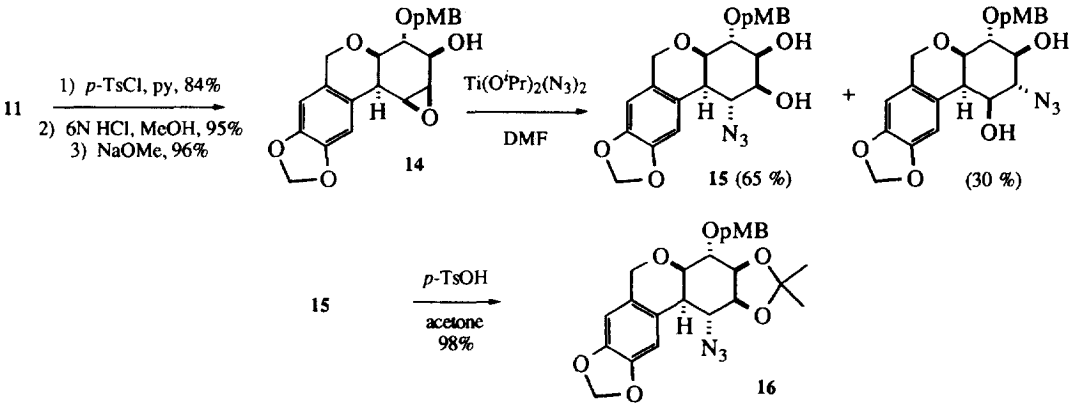
Scheme 4



Reasoning that the E2 elimination process would be less competitive for an epoxide ring-opening process due to lesser degree of antiperiplanarity of the C-10b proton and the oxygen leaving group at C-4a, we generated the epoxide **14** in high yield by a three-step sequence: tosylation of the C4a hydroxyl of **11**, removal of the cyclohexylidene ketal with HCl in MeOH, and then treatment with sodium methoxide in MeOH to close the

epoxide (Scheme 5). In the event, the critical epoxide opening with NaN_3 proceeded smoothly to give a 1:1 mixture of separable regioisomers.[18] Treatment of the epoxide with $Ti(O\text{-}^iPr)_2(N_3)_2$,[19] however, provided a 2:1 mixture of regiosiomers, from which the desired isomer **15** was isolated in 65% yield. To facilitate structure proof, **15** was converted to the acetonide **16**, which was fully characterized spectroscopically.[20]

Scheme 5



Diol **15**, prepared in 11 steps from *myo*-inositol, represents a highly advanced intermediate wherein the C-ring is fully elaborated in terms of both stereochemistry and functionality. From this intermediate, access to the pancratistatin skeleton requires oxidation of the benzylic C_6 carbon in the dihydropyran ring to give the lactone, reduction of the azide, and rearrangement of the lactone to the thermodynamically-favored lactam.[21] The brevity and operational simplicity of this approach, combined with the potential to employ enantiomerically-pure *myo*-inositol ketals as starting materials,[22] suggests that the synthetic route described above may be generally useful for the preparation of pancratastatin and its analogs.

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References and Notes

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12. For an example of regioselective epoxide opening of epoxide **3** with lithium aluminum hydride, see: Suami, T.; Ogawa, S.; Ueda, T.; Uchino, H. *Bull. Chem. Soc. Japan* **1972**, *45*, 3226.

13. To the best of our knowledge, only a single previous example of a 6-exo epoxy cyclialkylation of an aryl anion has been reported: Shankaran, K.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 5022.

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15. Data for **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J=8.4 Hz, 2H, Ar-H), 6.87 (d, J=8.4 Hz, 2H, Ar-H), 6.81 (s, 1H, Ar-H), 6.47 (s, 1H, Ar-H), 5.92 (d, J=1.1 Hz, 1H, O-CH-O), 5.91 (d, J=1.1 Hz, 1H, O-CH-O), 4.75 (d, J=15.0 Hz, 1H, Bn-H), 4.72 (d, J=11.0 Hz, 1H, Bn-H), 4.69 (d, J=15.0 Hz, 1H, Bn-H), 4.66 (d, J=11.0 Hz, 1H, Bn-H), 4.33 (dd, J=6.4, 5.7 Hz, 1H, C-H), 4.24 (dd, J=7.3, 6.4 Hz, 1H, C-H), 4.33 (t, J=3.3 Hz, 1H, C-H), 3.89 (m, 1H, C<u>H</u>-OH), 3.85 (dd, J=5.7, 3.3 Hz, 1H, C-H), 3.80 (s, 3H, OMe), 2.58 (dd, J=11.0, 3.3 Hz, 1H, C-H), 2.10 (br s, 1H, OH), 1.6 (m, 8H, cyclohexyl), 1.4 (br s, 2H, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 146.9, 145.9, 130.1, 129.5, 127.7, 125.4, 113.8, 111.0, 110.3, 104.2, 100.9, 79.9, 78.4, 76.6, 76.1, 72.4, 68.1, 55.3, 49.3, 39.5, 37.7, 35.1, 25.1, 24.0, 23.6; IR (neat) 3448, 3001, 2935, 2862, 1612, 1511, 1477, 1250, 1115, 1092, 1038, 933, 732 cm^{-1}; MS *m/e* calc'd for (CI M$^+$) $C_{28}H_{32}O_8$: 496.2097, found 496.2088.

16. Treatment of the alcohol precursor to **12** with diphenylphosphorylazide also yielded elimination product **13**; Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977.

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20. Data for **16**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J=8.8 Hz, 2H, Ar-H), 6.88 (d, J=8.8 Hz, 2H, Ar-H), 6.77 (s, 1H, Ar-H), 6.46 (s, 1H, Ar-H), 5.94 (d, J=1.2 Hz, 1H, O-CH-O), 5.93 (d, J=1.2 Hz, 1H, O-CH-O), 4.86 (d, J=15.0 Hz, 1H, Bn-H), 4.76 (d, J=15.0 Hz, 1H, Bn-H), 4.63 (d, J=11.4 Hz, 1H, Bn-H), 4.60 (d, J=11.4 Hz, 1H, Bn-H), 4.31 (dd, J=5.5, 3.3 Hz, 1H, C-H), 4.23 (dd, J=8.8, 5.5 Hz, 1H, C-H), 3.98 (dd, J=3.3, 2.9 Hz, 1H, C-H), 3.92 (dd, J=2.9, 2.2 Hz, 1H, C-H), 3.80 (s, 3H, OMe), 3.73 (dd, J=11.7, 8.8 Hz, 1H, N_3C-H), 2.54 (dd, J=11.7, 2.2 Hz, 1H, ArC-H), 1.55 (s, 3H, Me), 1.39 (s, 3H, Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 147.2, 146.1, 129.6, 129.5, 127.2, 125.9, 113.9, 110.8, 109.6, 104.0, 101.0, 78.7, 76.3, 75.9, 75.2, 72.6, 68.8, 65.1, 55.3, 37.9, 28.2, 25.9; IR (neat) 2920, 2106, 1612, 1512, 1484, 1242, 1076, 1038, 910, 864, 822, 733 cm^{-1}; MS *m/e* calc'd for (CI M$^+$) $C_{22}H_{23}O_7N_3$: 481.1849, found 481.1843.

21. For precedent for the lactone to lactam rearrangement, see refs. 10 (b) and 10 (c).

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