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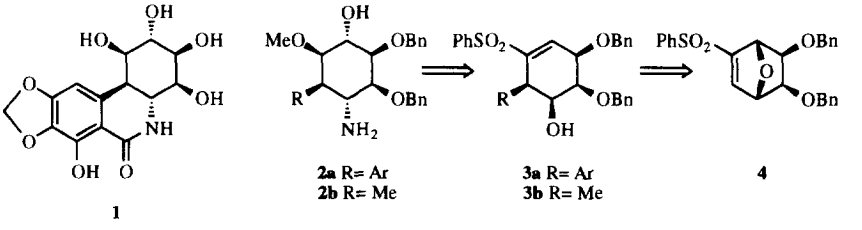
A Convenient Approach to the Aminocyclitol Fragment of Pancratistatin from 7-Oxanorbornenes

José Luis Aceña, Odón Arjona,* Fátima Iradier and Joaquín Plumet.*

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain.

Abstract: A totally stereoselective route to an analogue aminocyclitol fragment of the alkaloid pancratistatin has been achieved starting from a 7-oxanorbornenic disulfone. The key step was the alkylative cleavage of the oxygen bridge to produce a highly oxygenated cyclohexenyl sulfone.

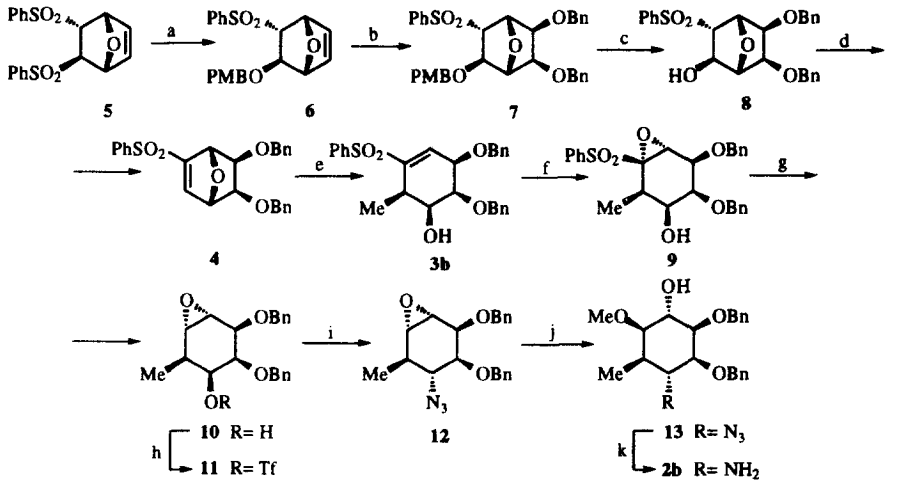
Pancratistatin **1** is a prominent member of the *Amaryllidaceae* alkaloids family exhibiting potent antitumor activities.[1] The current high level of interest in pancratistatin is reflected in the large number of synthetic efforts[2] although only two total syntheses,[3] one of them in racemic form,[3a] have been reported. In connection with our interest in cyclitol synthesis from 7-oxanorbornene derivatives,[4] we have developed an approach to the aminocyclitol moiety of pancratistatin **2** using as a key step the oxygen bridge opening of the 7-oxanorbornenic sulfone **4** by means of the S_N2' reaction[5] with the appropriate organolithium reagent to produce **3** (Scheme 1). In this communication we wish to report the synthesis of the analogue aminocyclitol **2b** using as a model reaction the ring opening of **4** with MeLi.



1 **2a** R= Ar **2b** R= Me **3a** R= Ar **3b** R= Me **4**

Scheme 1

The starting vinyl sulfone **4** was obtained from the known disulfone **5**[6] in five steps as follows (Scheme 2). Reaction of **5** with KOH and *p*-$MeOC_6H_4CH_2OH$ (PMBOH)[7] afforded **6**[8] which was osmylated and dibenzylated to give **7**. Deprotection of the PMB group gave alcohol **8**. Mesylate formation and elimination finally produced **4** in 56% overall yield from **5**. According to our previously proposed procedure,[5] addition of 1.5 equiv of MeLi to **4** gave rise to the oxygen bridge cleavage producing the cyclohexenyl sulfone **3b** in good yield. Its nucleophilic epoxidation with LiOO*t*-Bu yielded **9** as the only diastereoisomer. In contrast with our previous results,[4b] the stereoselectivity of this epoxidation was not controlled by the free homoallylic hydroxyl group probably due to the higher steric hindrance of the β face. Subsequent desulfonylation of **9** afforded oxirane **10**. Inversion of the corresponding triflate **11** by treatment with *n*-Bu_4NN_3[4c] gave the azide **12**. Finally, the regioselective methanolysis of the epoxide with catalytic DDQ[9] produced **13** which was selectively hydrogenated[10] to the amine **2b**.



Reagents and conditions: a) KOH, PMBOH, MeCN, rt, 12 h. b) 1) OsO_4, NMe_3O, Me_2CO/H_2O 8:1, rt, 48 h, 83% from **5**. 2) NaH, BnBr, *n*-Bu_4NI (cat.), THF, rt, 6 h, 89%. c) DDQ (1.5 equiv) CH_2Cl_2/H_2O 20:1, rt, 12 h, 92%. d) Et_3N, MsCl, CH_2Cl_2, 0 °C, 30 min, then DBU, 0 °C, 30 min, 83%. e) MeLi (1.5 equiv), THF, -78 °C, 1 h, 85%. f) *t*-BuOOH, *n*-BuLi, THF, -78 °C to rt, 48 h, 80%. g) Na-Hg, Na_2HPO_4, MeOH/THF 1:1, -20 °C to rt, 6 h, 94%. h) Tf_2O, pyr, CH_2Cl_2, 0 °C, 30 min. i) *n*-Bu_4NN_3, PhH, rt, 30 min, 83% from **10**. j) DDQ (0.5 equiv), MeOH, 60 °C, 6 h, 78%. k) H_2, Pd-C, AcONa (cat.), 2 h, 30%.[10]

Scheme 2

In summary, an efficient route to an analogue aminocyclitol fragment of pancratistatin, with the correct configuration of its six stereogenic centers, has been accomplished in a totally stereoselective manner. The synthesis of pancratistatin itself in nonracemic form,[11] by using a suitable aryllithium reagent in the bridge opening reaction, is currently being pursued in our laboratory.

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8. All new compounds showed spectroscopic and analytical data consistent with the assigned structures. In the case of ^1H NMR, selective decoupling experiments were used for stereochemical determinations.
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11. Alcohol **8** has been resolved by treatment with (-)-camphanic chloride and subsequent diastereomeric separation by column chromatography. Determination of the absolute configuration of each enantiomer is now under progress.

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