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Formal Synthesis of (±)-Platensimycin

Yefen Zou, **Chun-Hsing Chen**, **Christopher D. Taylor**, **Bruce M. Foxman**, and **Barry B. Snider**
Department of Chemistry MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

Abstract

Reductive alkylation of 5-methoxy-1-tetralone (6) with 2,3-dibromopropene gave an equilibrium mixture of bicyclic diones 7 (51%) and 8 (35%). Radical cyclization of 7 afforded tricyclic dione 5 (84%), which was reduced, cyclized and dehydrated to give tetracyclic alkene 13 in 63% yield. Allylic oxidation of 13 with SeO_2 and activated MnO_2 afforded enone 2 in 85% yield, thereby completing a short formal synthesis of (±)-platensimycin.

The broad spectrum antibiotic platensimycin (**1**) (see Scheme 1) was recently isolated by a Merck group from *Streptomyces platensis* as part of a screening program designed to isolate inhibitors of bacterial fatty acid biosynthesis by the highly conserved condensing enzyme FabF.[1] Only the weak antibiotics cerulenin and thiolactomycin were known to act by this mechanism. Potent inhibitors of this enzyme are expected to be antibiotics with no cross-resistance to existing drugs. Platensimycin acts by specific binding with the acyl-enzyme intermediate of FabF. The structure and absolute stereochemistry of platensimycin were determined by a combination of spectroscopic methods and X-ray crystallography of a bromo derivative.[1]

We thought that the acyl portion of platensimycin should be readily accessible by introduction of a methyl group and a propanoic acid side chain onto enone **2**. Nicolaou recently reported the first synthesis of platensimycin (**1**) in which he prepared **2** in 10 steps and elaborated it to (±)-platensimycin (**1**).[2] We planned to prepare **2** by dehydration of the alcohol of **3** and allylic oxidation. Acid-catalyzed cyclization of unsaturated diol **4** should afford the ether linkage of **3**. L-Selectride reduction of dione **5** should provide the bis axial alcohol **4** (see Scheme 1).

This approach was attractive because Marinovic reported a two-step synthesis of dione **5** in 1983.[3] Reductive alkylation of 5-methoxy-1-tetralone (**6**) with 2,3-dibromopropene by Narisada's procedure[4] afforded bicyclic diones **7** and **8** in 68% yield with unspecified stereochemistry (see Scheme 2). Radical cyclization of this mixture of **7** and **8** with *n*-Bu_3SnH in benzene at reflux afforded the tricyclic diones **5** and **9** in 85% yield, again with unspecified stereochemistry.

Although this route is very short, it is only attractive if the desired tricyclic dione **5** can be prepared cleanly and in good yield. Unfortunately, molecular mechanics calculations[5] suggested that the desired tricyclic dione **5** is 1.6 kcal/mol less stable than epimeric dione **9**. However, calculations also suggested that the desired bicyclic dione **7** is 0.1 kcal/mol more stable than epimeric dione **8**. Therefore, it might be possible to isolate **7** in acceptable yield and convert it to **5** if the radical cyclization can be carried out without epimerization.

In our hands, the reduction of **6** was best carried out with potassium in NH_3/Et_2O at -78 °C.[6] Addition of LiBr and then 2,3-dibromopropene effected alkylation. Hydrolysis of the enol ether with conc HCl in THF for 30 min afforded a readily separable mixture from which the desired

snider@brandeis.edu

bicyclic dione **7** was isolated 51% yield and the epimer **8** was obtained in 35% yield. The structures of **7** and **8** could not be assigned at this point so both compounds were carried on. The HCl hydrolysis step produced close to an equilibrium mixture. Acid catalyzed equilibration of either **7** or **8** provided a 4:3 mixture of **7** and **8**. Equilibration of **8** afforded additional **7** (19%), which was therefore isolated in 70% overall yield from 5-methoxy-1-tetralone (**6**).

Radical cyclization of **7** with *n*-Bu_3SnH and catalytic AIBN in benzene at reflux afforded the desired tricyclic dione **5** in 84% yield without any epimerization. This practical two-step route to **5** proceeds in 59% overall yield. A similar sequence converted the undesired bicyclic dione **8** to tricyclic dione **9** in 81% yield. Equilibration of either **5** or **9** with KOH in MeOH gave a 1:4 mixture of **5** and the more stable tricyclic dione **9**. The equilibration of both bicyclic diones **7** and **8** and tricyclic diones **5** and **9** thus gave results close to those expected from molecular mechanics calculations.

The ^1H NMR spectra of **5** and **7**-**9** were hard to analyze because of extensive overlap. Fortunately, all the hydrogens of **5** could be resolved in C_6D_6 at 800 MHz and the stereochemistry of **5** was tentatively assigned based on an NOE between the ring fusion hydrogen and one of the allylic methylene hydrogens (see Figure 1). The stereochemical assignments of **5** and **7**-**9** were unam-biguously established by X-ray crystal structure determination of both tricyclic diones **5** and **9** (see Figure 1).

L-Selectride reduction of the unhindered ketone of **5** occurred readily at -78 °C, but gave a 1:1 mixture of equatorial and axial alcohols. The other ketone was reduced at 25 °C affording a 12:1 mixture favoring the desired axial alcohol. This resulted in the formation of an inseparable 1:1 mixture of **4** and **11** in 90% yield (see Scheme 3).[7] This mixture was treated with TFA and CH_2Cl_2 to effect formation of the ether linkage as described by Nicolaou[2] for a related substrate with different functionality in the isolated ring. This two-step sequence afforded axial alcohol **3** in 39% yield and the equatorial alcohol **12** in 42% yield from the mixture of diols. Treatment of the axial alcohol **3** with Tf_2O and pyridine in CH_2Cl_2 afforded the triflate, which eliminated readily to give alkene **13** in 90% yield. Similar treatment of the equatorial alcohol **12** afforded triflate **14**, which did not undergo E2 elimination readily because there is no β-hydrogen anti to the triflate.[8] Eventually, we found that treatment of crude triflate **14** with either silica gel or hydrochloric acid resulted in clean elimination, possibly by an E1 mechanism, to form alkene **13** in 84% yield from **12**.[9] This three-step sequence converts tricyclic dione **5** to tetracyclic alkene **13** in 63% overall yield, but diols **4** and **11** cannot be characterized.

Alternatively, reduction of dione **5** with $NaBH_4$ in EtOH at -78 to 0 °C afforded equatorial keto alcohol **10**. Reduction of **10** with L-Selectride afforded diol **11** contaminated with a few percent of the equatorial alcohol[7] in 83% yield. Acid catalyzed cyclization afforded **12** (90%), which was elaborated to **13** as previously described. This four-step sequence converts tricyclic dione **5** to tetracyclic alkene **13** in 55% overall yield.

Allylic oxidation of alkene **13** with CrO_3·3,5-dimethylpyrazole[10] in CH_2Cl_2 at -25 °C provided an inseparable 4:1 mixture of the desired enone **2** and the regioisomer **15** in 75% yield (see Scheme 4). Oxidation of **13** with CrO_3·pyridine was slower, but gave the same ratio of products. The formation of mixtures of products was expected[11] because both ends of the intermediate allylic cation are secondary.

We therefore turned to SeO_2 oxidation, which should be regiospecific because the oxygen is introduced by an ene reaction followed by a [2,3]-sigmatropic rearrangement.[12] Oxidation of **13** with 8 equiv of SeO_2 in dioxane at 140 °C in a microwave reactor for 30 min afforded allylic alcohol **17** in only 27% yield. The major product was dienone **16** (59%). Oxidation of alkene **13** with SeO_2 should give allylic alcohol **17** and enone **2**, which is apparently oxidized further to dienone **16** as has been observed in related systems.[13] Oxidation of alkene **13** with only 3

equiv of SeO_2 in dioxane at 110 °C in a microwave reactor for only 10 min afforded allylic alcohol **17** in 83% yield and enone **2** in 7% yield. Oxidation of alcohol **17** with activated MnO_2 provided enone **2** in 94% yield. This two-step sequence converts alkene **13** to enone **2** in 85% yield. The ^{1}H and ^{13}C NMR spectra of **2** are identical to those reported by Nicolaou.

In conclusion, we have developed an efficient route (seven steps, 32% overall yield) to tetracyclic enone **2**, a late intermediate in Nicolaou's (±)-platensimycin (**1**) synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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7. This mixture contained a few percent of the epimers of **4** and **11** with an equatorial alcohol in the bicyclic moiety. These isomers cannot form an ether on treatment with TFA and are easily separated from **3** and **12**.

8. Atempted dehydration of **12** with Burgess' reagent, Martin sulfurane, or via the mesylate failed.

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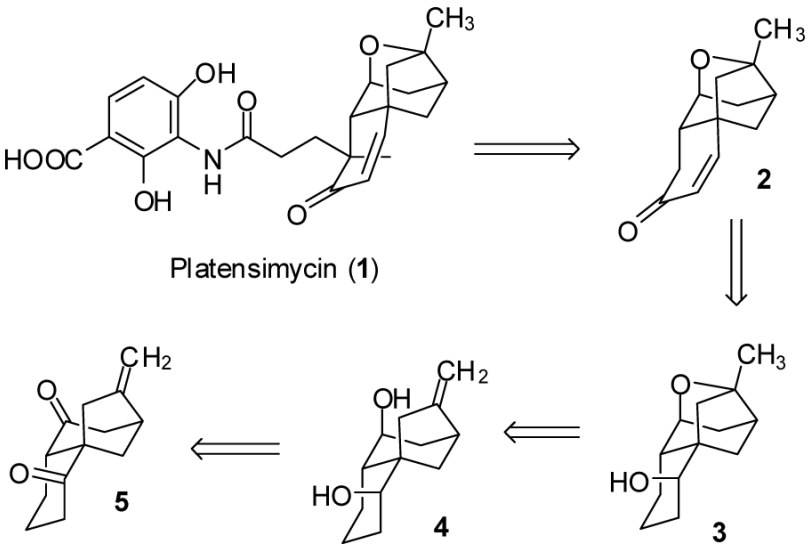
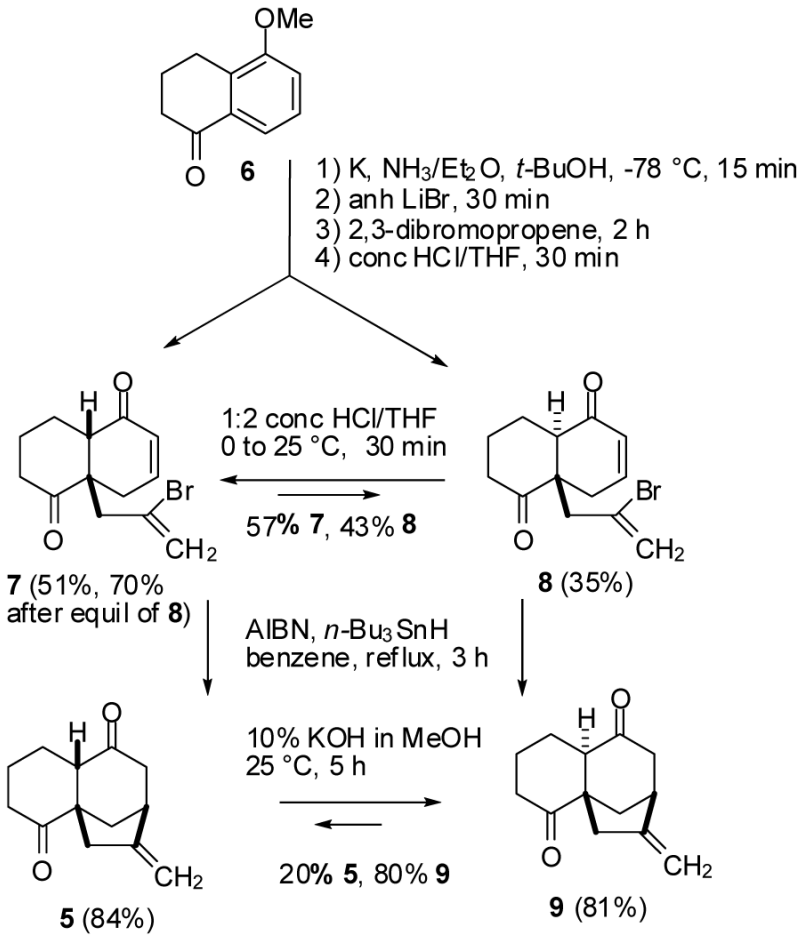
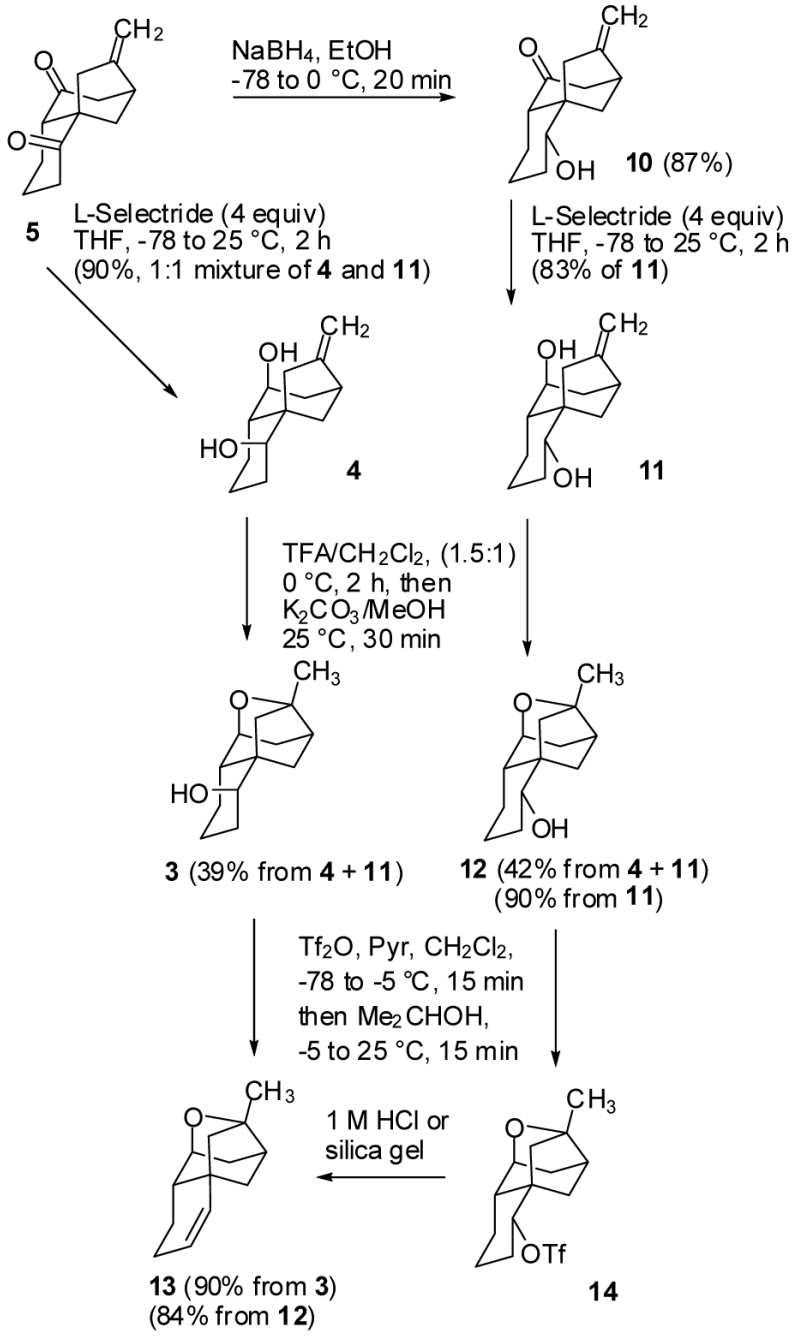


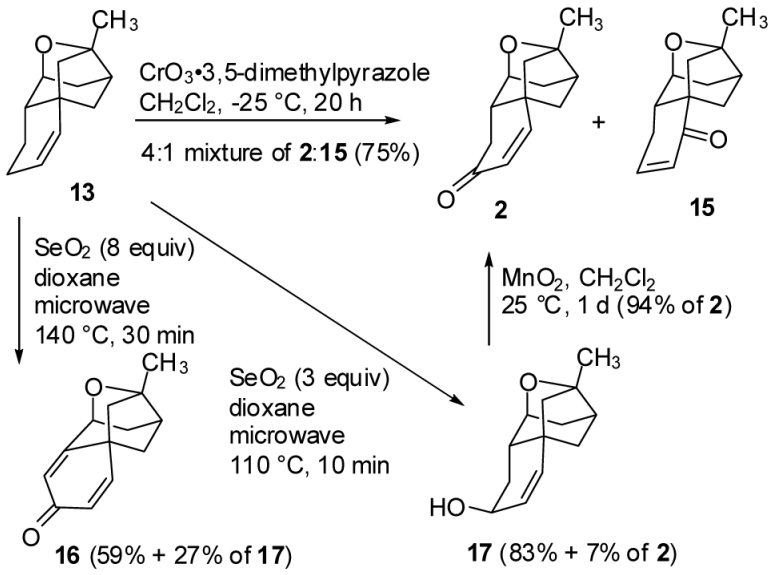
Scheme 1.
Retrosynthesis of Platensimycin



Scheme 2.
Synthesis of Tricyclic Diones **5** and **9**



Scheme 3.
Reduction, Cyclization and Dehydration of **5**



Scheme 4.

Allylic Oxidation of **13** to Give Enone **2**

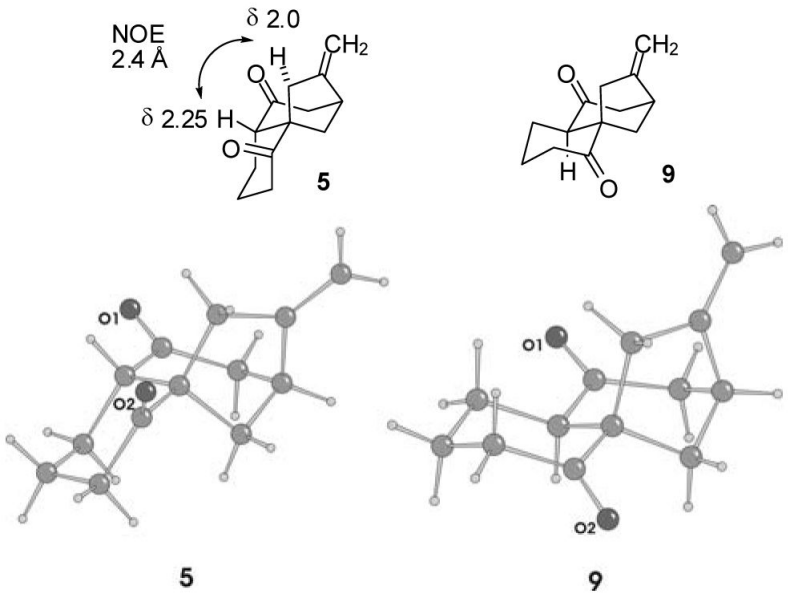


Figure 1.
Three Dimensional Representations and Molecular Structures of **5** and **9** Established by X-ray Structure Determination.