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Formal Synthesis of (±)-Platensimycin

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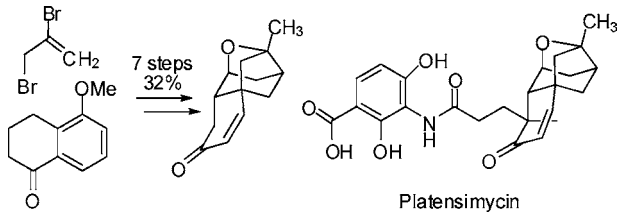
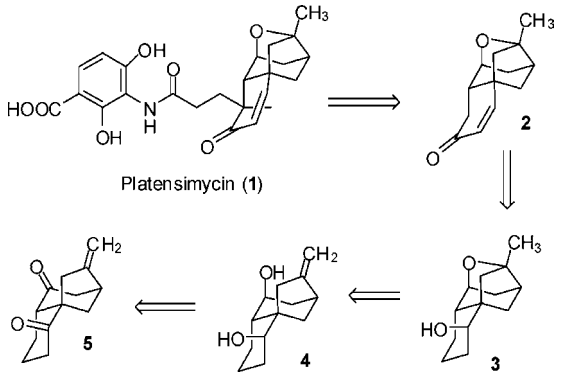
ABSTRACT



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*

Scheme 1. Retrosynthesis of Platensimycin



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 axial alcohol of **3** and allylic oxidation. Acid-catalyzed cyclization of unsaturated diol **4** should afford the ether linkage of **3**.

(1) (a) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Allocco, J.; Basilio, A.; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *Nature* **2006**, *441*, 358−361. (b) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am. Chem. Soc.* **2006**, *128*, 11916−11920. (c) Häbich, D.; von Nussbaum, F. *ChemMedChem* **2006**, *1*, 951−954.

(2) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086−7090.

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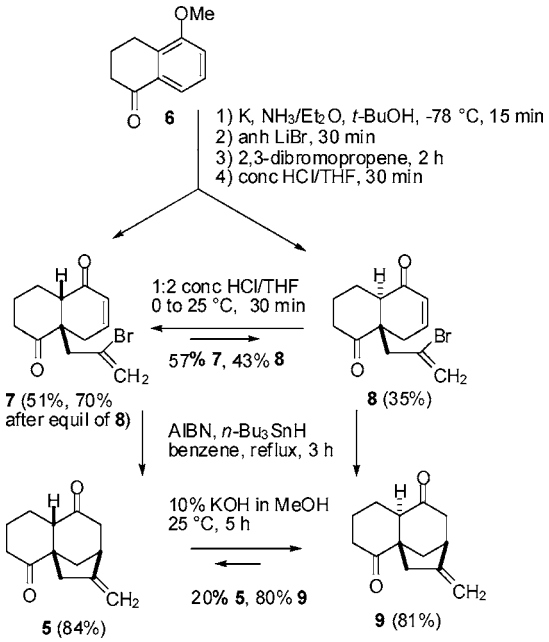
L-Selectride reduction of dione **5** should provide the bis axial alcohol **4** (see Scheme 1).

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).

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



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 concentrated HCl in THF for 30 min afforded a readily separable mixture from which the desired bicyclic dione **7** was isolated in 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 on the basis of 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 unambiguously established by X-ray crystal structure determination of both tricyclic diones **5** and **9** (see Figure 1).

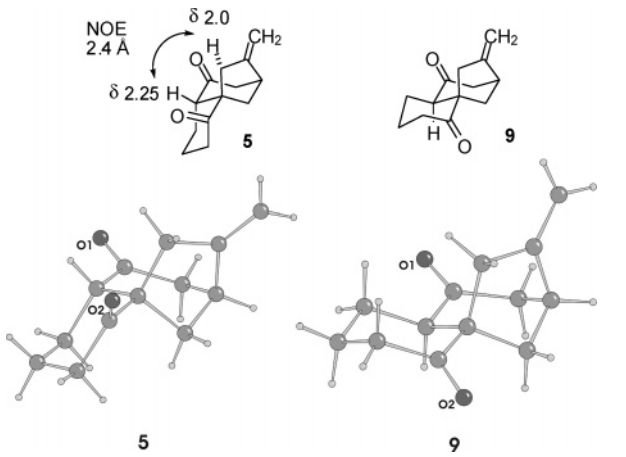


Figure 1. Three-dimensional representations and molecular structures of **5** and **9** established by X-ray structure determination.

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

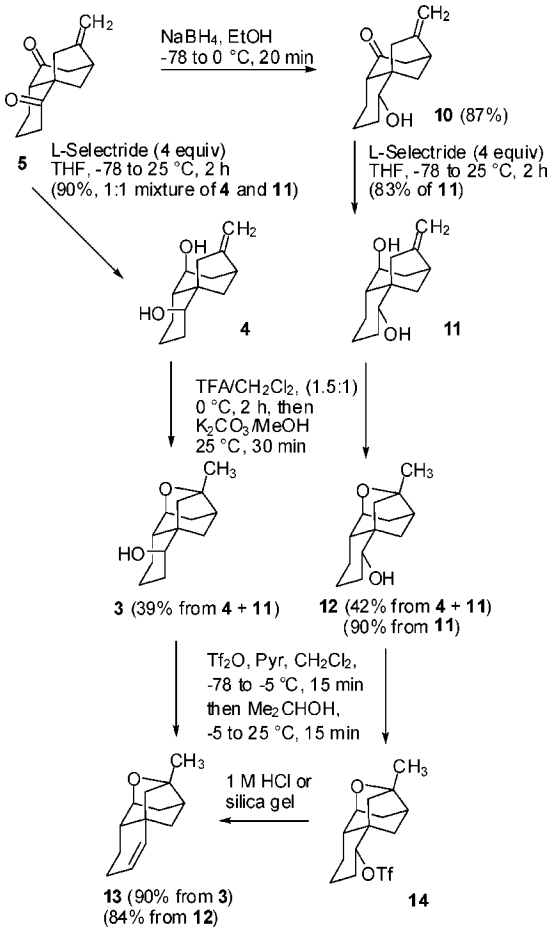
(3) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871−1874.

(4) (a) Narisada, M.; Watanabe, F. *J. Org. Chem.* **1973**, *38*, 3887−3892. (b) Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984−3986.

(5) PCMODEL version 8.0 from Serena Software was used with MMX.

(6) For more recent studies of this reductive alkylation, see: (a) Labadie, G. R.; Estiú, G. L.; Cravero, R. M.; Gonzalez Sierra, M. *THEOCHEM* **2003**, *635*, 173−182. (b) Marcinow, Z.; Rabideau, P. W. *J. Org. Chem.* **1988**, *53*, 2117−2119. (c) Labadie, G. R.; Cravero, R. M.; Gonzalez-Sierra, M. *Synth. Commun.* **2000**, *30*, 4065−4079.

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

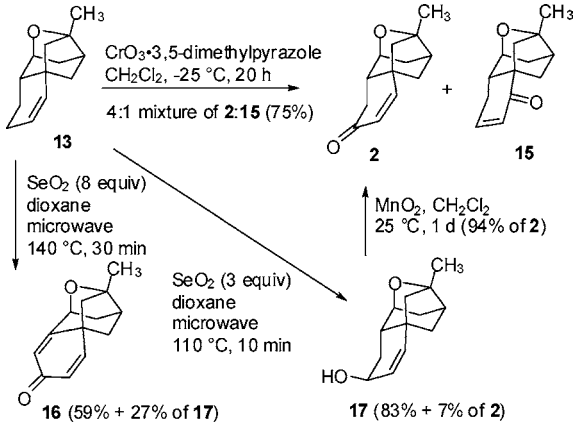


two-step sequence afforded axial alcohol **3** in 39% yield and the equatorial alcohol **12** in 42% yield from the mixture of diols. Treatment of the axial alcohol **3** with Tf_2O and pyridine in CH_2Cl_2 afforded the triflate, which eliminated readily to give alkene **13** in 90% yield. Similar treatment 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·

Scheme 4. Allylic Oxidation of **13** to Give Enone **2**



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 ^1H and ^{13}C NMR spectra of **2** are identical to those reported by Nicolaou.

(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) Attempted dehydration of **12** with Burgess' reagent, Martin sulfurane, or via the mesylate failed.

(9) LiCl in THF has been reported to facilitate elimination of triflates: Finch, H.; Harwood, L. M.; Highcock, R.; Jackson, B.; Prout, K.; Robertson, G.; Sewell, R. C. *Synlett* **1990**, *7*, 384−386.

(10) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057−2059.

(11) (a) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587−3592. (b) Gulge, R.; Shaligram, A. M. *Indian J. Chem., Sect. B* **1985**, *24B*, 815−819. (c) Engler, T. A.; Sampath, U.; Velde, D. V.; Takusagawa, F. *Tetrahedron* **1992**, *48*, 9399−9416. (d) Zhao, J.; Zhao, F.; Wang, Y.; Li, H.; Zhang, Q.; Guénard, D.; Ge, Q.; Wei, E.; Jiang, H.; Wu, Y.; Wang, L.; Jiang, H.; Guéritte, F.; Wu, X.; Cheng, C. H. K.; Lee, S.-S.; Zhao, Y. *Helv. Chim. Acta* **2004**, *87*, 1832−1853.

(12) (a) Rabjohn, N. *Org. React.* **1976**, *24*, 261−415. (b) Bullman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Ley, S. V., Ed.; Pergamon Press: New York, 1991; Vol. 7, pp 83−117.

(13) Kocór, M.; Tuszy-Maczka, M. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1961**, *9*, 405−409; *Chem. Abstr.* **1964**, *60*, 6910e or 38978. (b) Moreno-Dorado, F. J.; Guerra, F. M.; Aladro, F. J.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron* **1999**, *55*, 6997−7010.

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.

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Supporting Information Available: Complete experimental procedures, copies of ^{1}H NMR, NOESY, and ^{13}C NMR spectral data, and X-ray crystallographic data (CIF files) for **5** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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