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Concise Formal Total Synthesis of Platensimycin Mediated by a Stereoselective Autoxidation and Hydroxyl Group Directed Conjugative Reduction

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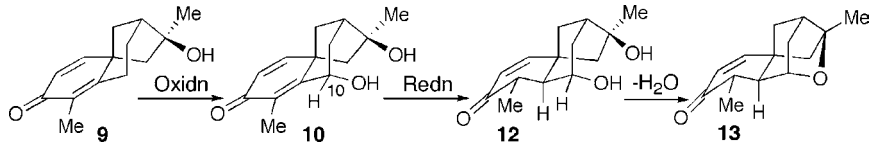
ABSTRACT



The synthesis of 13, an advanced intermediate in the Nicolaou synthesis of platensimycin 1, was made from 9 by autoxidation to give 10, which was stereoselectively reduced providing 12. Finally, dehydration of 12 by heating in DMSO resulted in 13.

The structure[1] and broad spectrum antimicrobial activity[2] of platensimycin **1** has rapidly attracted considerable attention from the organic synthesis community.[3] The retrosynthesis for **1** involves the cross-conjugated 2,5-cyclohexadieneone **2** formed from the intramolecular carbenoid insertion of **3**, Figure 1.[4] The acid **4** is available in both R- and S-enantiomeric enriched forms from the microbial reduction of the corresponding 1-tetralone-2-carboxyethyl esters followed by hydrogenolysis of the benzylic hydroxyl group.[5]

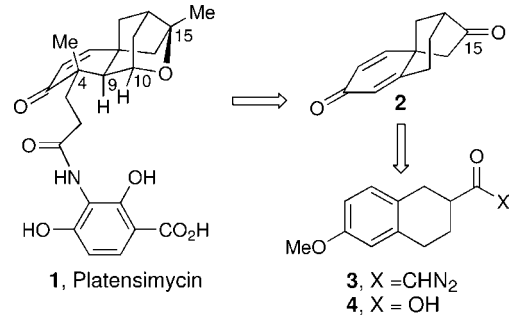


Figure 1. Retrosynthetic analysis of platensimycin **1**.

The recent reports by Mulzer[3i,t] and Corey[3j] concerning the conversion of **2** into **6**, and **5** into **6** respectively, and the subsequent reduction of **6** and dehydrogenation to give **7** as a mixture of stereoisomers at C-9 (40:1, Mulzer), a pivotal intermediate in the Nicolaou synthesis of both (±)-**1**[3a] and

† Author for inquiries concerning the X-ray data.

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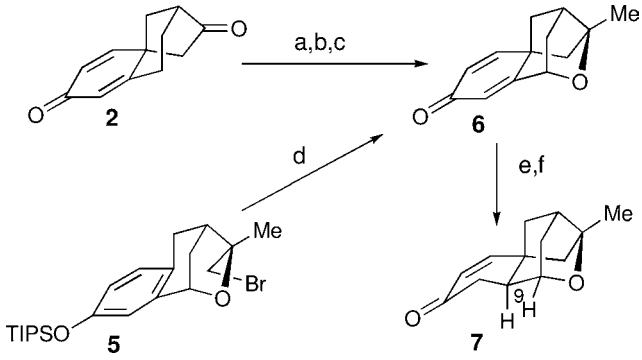
Scheme 1. Mulzer's and Corey's Route To form **6** and **7**[a]



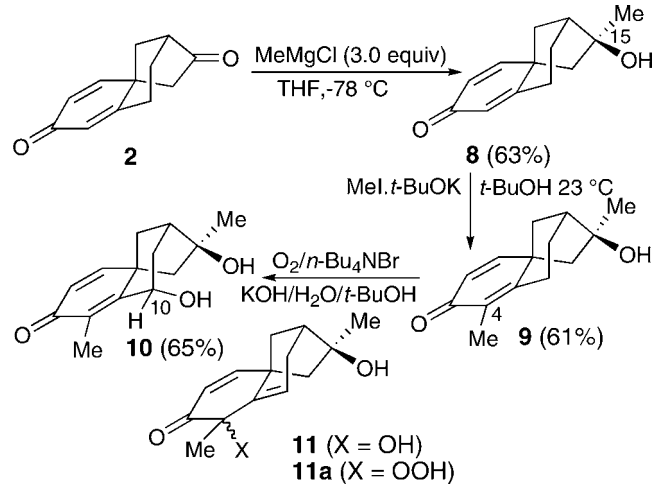
[a] Reaction conditions: (a) MeMgI, THF, −78 °C, 4 h (71% brsm); (b) NBS, $(BzO)_2$, CCl_4, reflux (75%); (c) NaOMe, THF, 0 °C (80%); (d) *n*-Bu_4NF, THF, 130 °C (88%); (e) Mulzer's conditions: (i) cat. Ir-cat 1,[3t] H_2, 84%; (ii) HIO_3•DMSO, DMSO, cyclohexene (60%), 1.3:1 epimers at C-9 (major isomer shown); (f) Corey's conditions: (i) $[Rh(cod)_2]BF_4$,(*R*,*R*)-DIOP, H_2 600 psi (72%); (ii) TMSOTf, Me_3N, followed by IBX, MPO, DMSO (80%) (small amount of C-9 epimer).

(−)-**1**,[3b] Scheme 1, prompted this report. In this letter we describe the use of **2** as a key intermediate in the formal total synthesis of platensimycin **1** that avoids the above strategy and leads to **13** (Scheme 3) in a completely stereoselective sequence.

We have explored an alkylation and autoxidation strategy as depicted in Scheme 2. The final product **10** only requires a hydroxyl directed stereospecific conjugated reduction of the tetrasubstituted dienone double bond, followed by formation of the tetrahydrofuran ring to complete a formal synthesis of platensimycin.[3a,b]

Treatment of **2** with MeMgCl (3.0 equiv) in THF at −78 °C resulted in the complete consumption of **2** and the formation of **8** (63%).[3i] Whereas, treatment of **2** with MeLi (excess) in THF at −78 °C also gave **8** (ca. 30%) along with recovered **2**. Quenching the above reaction at −78 °C with D_2O resulted in the incorporation of one deuterium atom α- to the cyclopentanone carbonyl group in recovered **2**, thus indicating, as suspected, that enolization of **2** by MeLi is the deleterious pathway that drastically reduces the yield of **8**.

Scheme 2. C-4 Alkylation and C-10 Autoxidation



Treatment of **8** with *t*-BuOK/*t*-BuOH/MeI gave **9** (61%), with no detectable amounts of any geminal dimethylation product. It was found that exposure of **9** to O_2 and *n*-Bu_4NBr/KOH/H_2O/*t*-BuOH[6,7] gave **10** (65%) as a single stereoisomer whose structure was established by single X-ray crystallography, Figure 2. When the autoxidation process was conducted at −78 °C in the presence of $P(OMe)_3$, the α-hydroxyenone **11** (8%) was also isolated. It appears likely that **10** arises from **11a** by rearrangement of the intermediate

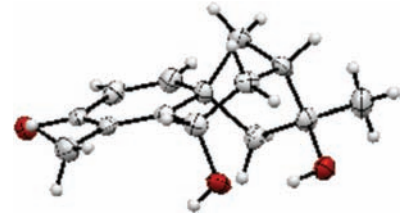


Figure 2. ORTEP of **10**.

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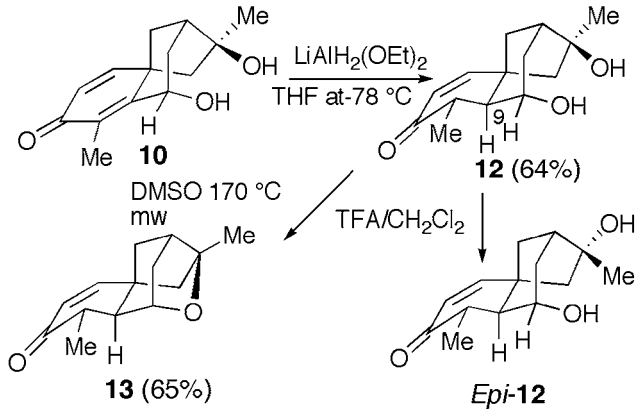
(7) For autoxidation of α,β-unsaturated ketones, see: (a) Shimizu, T.; Hiranuma, S.; Yoshioka, H. *Chem. Pharm. Bull* **1989**, *37*, 1963–1965. (b) Aladro, F. J.; Guerro, F. M.; Moreno-Dorado, F. X.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron* **2001**, *57*, 2171–2178.

allylic hydroperoxide.[8] The stereochemistry of the newly introduced C-10 *sec*-hydroxyl group is the correct relative configuration.

Next, the possibility of selective reduction of the tetrasubstituted dienone double bond in **10** by conjugate hydride reduction directed from the C-10 hydroxyl group was examined. Eventually, it was found that treatment of **10** with $LiAlH_2(OEt)_2$ in THF at −78 °C cleanly gave **12** (64%) and recovered starting material (30%), Scheme 3. The desired

Scheme 3. Hydroxyl Directed Conjugate Reduction



stereochemistry at C-9 was confirmed by X-ray crystallography (Figure 3).

Despite the fact that **12** would appear to be readily converted into **13** by reported procedures,[3a−c] treatment of **12** with trifluoroacetic acid in CH_2Cl_2 gave small amounts

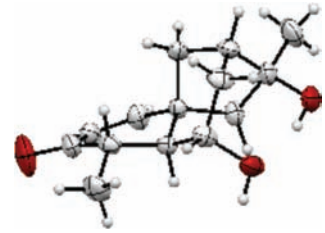


Figure 3. ORTEP of **12**.

of **13** and, interestingly, Epi-**12**. Since the ring cleavage of tetrahydrofurans with electrophilic reagents is well-known[9] and forms the basis of the synthesis, for example, of 4-chlorobutanol from THF, it is somewhat surprising that **12**/**13** would be stable to strongly electrophilic reagents.

In consequence, we treated the 1,3-diol **12** with dimethylsulfoxide[10] (as solvent, relatively neutral reaction conditions) under microwave conditions and obtained **13** in good yield.

The sequence of reactions from the known ketone **2** to **13** proceeds in five steps in an overall yield of 10% and is completely stereoselective.

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Supporting Information Available: Complete experimental details and compound characterization. This information is available free of charge via the Internet at http://pubs.acs.org.

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