Formal synthesis of (±)-platensimycin†

K. C. Nicolaou,*[ab] Yefeng Tang[a] and Jianhua Wang[a]

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A formal total synthesis of (±)-platensimycin [(±)-1] is reported involving an intramolecular Stetter reaction and a radical cyclization.

Platensimycin (**1**, Fig. 1), reported recently by scientists at Merck,[1] is a promising antibiotic. It has been shown to act through a new mechanism of action and is active *in vitro* against a range of human pathogenic bacterial strains, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Additionally, low mammalian toxicity and *in vivo* efficacy have also been demonstrated.[1] The remarkable biological profile and interesting chemical structure of platensimycin prompted us to initiate a synthetic program, which culminated in the total synthesis of the racemate,[2] and, more recently, the natural (−)-enantiomer of platensimycin (**1**).[3] We report here an alternative approach to the polycyclic core of platensimycin, leading to a formal total synthesis of (±)-**1**. This route involves an intramolecular Stetter reaction and a radical cyclization to form the key carbon–carbon bonds *en route* to the cage-like structure of the target molecule.

The retrosynthetic analysis that led to this approach is shown in Fig. 1. Thus, retrosynthetic cleavage of the amide bond of **1** followed by removal of the side chains left cage-like ketone **2** as a key intermediate.[2,3] Cleavage of the ether linkage led to tricyclic alcohol **3**, with a radical addition to an enone envisaged to form the [3.2.1] bicyclooctane structural motif. Finally, diketone **4** was expected to be available through an intramolecular Stetter reaction between a bis-enone motif and a pendant aldehyde.

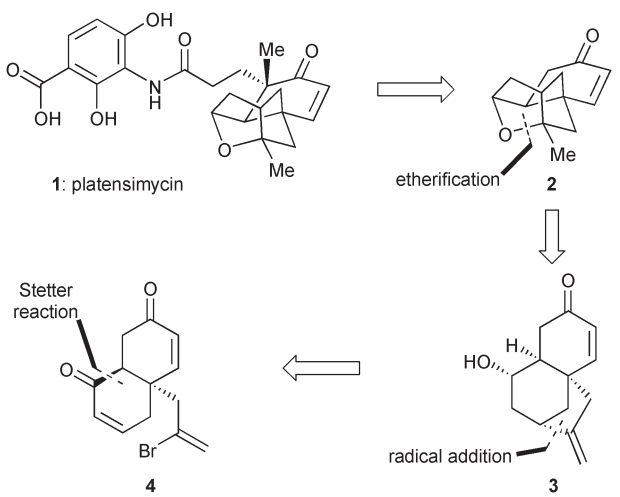
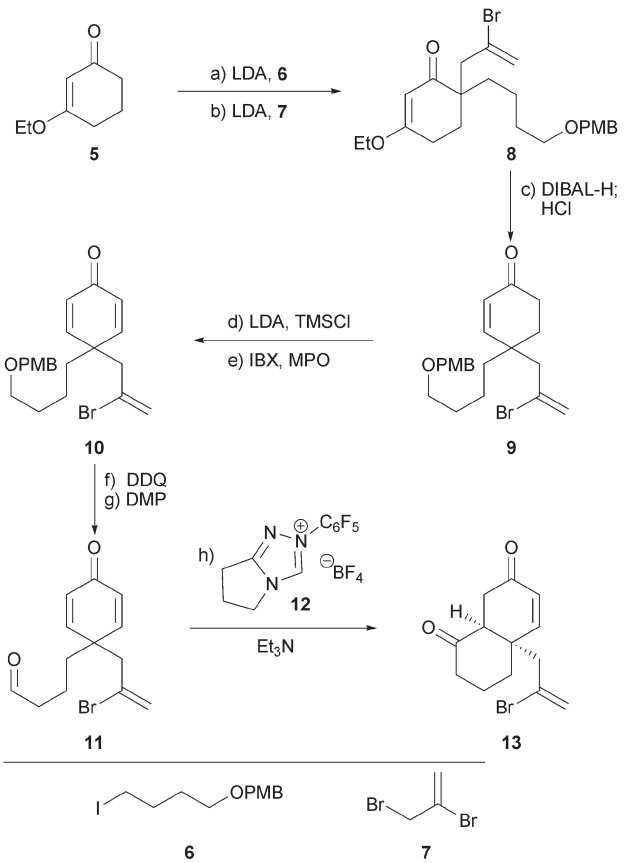


Fig. 1 Molecular structure and retrosynthetic analysis of platensimycin (**1**).

The preparation of the substrate required for the key Stetter reaction is summarized in Scheme 1. Alkylation of the lithium



Scheme 1 Synthesis of diketone **4**. *Reagents and conditions*: (a) LDA (1.3 equiv.), **6** (1.4 equiv.), THF–HMPA (5 : 1), −78 → 0 °C, 12 h, 75%; (b) LDA (1.3 equiv.), **7** (1.5 equiv.), THF–HMPA (5 : 1), −78 → 0 °C, 12 h, 87%; (c) DIBAL-H (1.5 equiv.), toluene, −78 → 0 °C, 2 h; then 1 N aq. HCl, 1 h, 92%; (d) LDA (1.1 equiv.), TMSCl (1.1 equiv.), THF, −78 → 0 °C, 1 h; (e) IBX (1.5 equiv.), MPO (1.5 equiv.), DMSO, 25 °C, 2 h, 77% for two steps; (f) DDQ (1.2 equiv.), CH_2Cl_2–H_2O (9 : 1), 25 °C, 1 h, 95%; (g) DMP (1.2 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, 25 °C, 2 h, 95%; (h) **12** (1.0 equiv.), Et_3N (6.0 equiv.), CH_2Cl_2, 45 °C, 4 h, 64%. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, DIBAL-H = diisobutylaluminium hydride, TMS = trimethylsilyl, IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine *N*-oxide, DMSO = dimethyl sulfoxide, DDQ = 2,3-dichloro-4,5-dicyano-1,4-benzoquinone, DMP = Dess–Martin periodinane.

[a]*Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California, USA 92037. E-mail: kcn@scripps.edu*
[b]*Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California, USA 92093*
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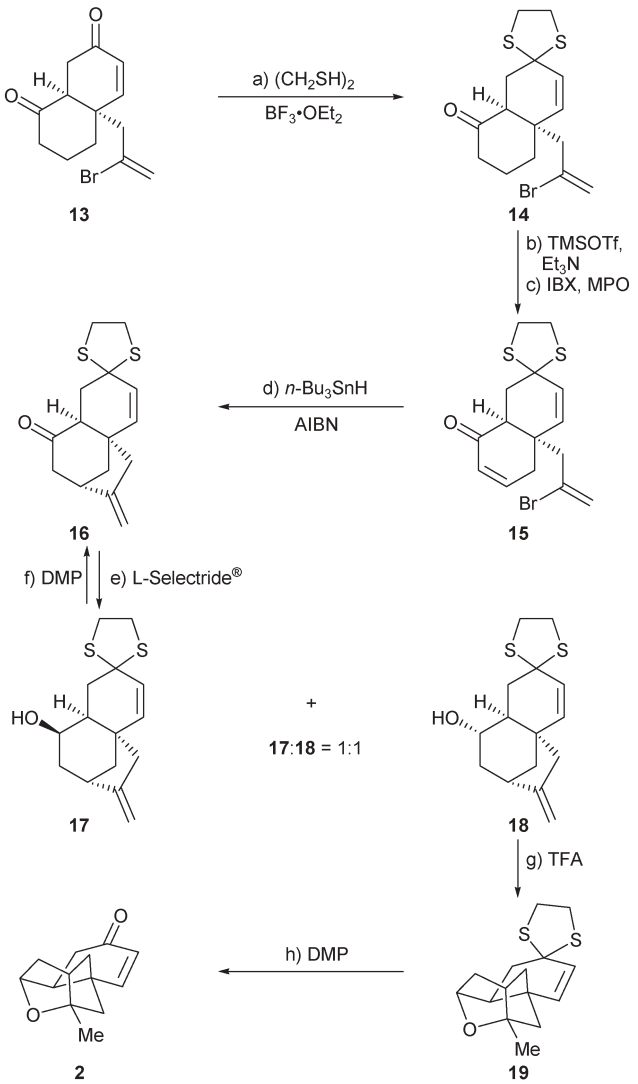

Scheme 2 Completion of the synthesis of cage structure **2**. *Reagents and conditions*: (a) ethanedithiol (2.0 equiv.), $BF_3{\cdot}OEt_2$ (1.5 equiv.), CH_3OH, 25 °C, 2 h, 80%; (b) TMSOTf (1.5 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2, 25 °C, 1 h; (c) IBX (2.0 equiv.), MPO (2.0 equiv.), DMSO, 25 °C, 2 h, 82% for two steps; (d) n-Bu_3SnH (4.0 equiv.), AIBN (0.5 equiv.), C_6H_6, reflux, 1 h, 86%; (e) L-Selectride® (4.0 equiv.), THF, −20 °C, 1 h, 91%, 1 : 1 dr; (f) DMP (1.2 equiv.), pyridine (6.0 equiv.), CH_2Cl_2, 25 °C, 1 h, 99%; (g) TFA–CH_2Cl_2 (2 : 1), 0 °C, 1 h, 90%; (h) DMP (8.0 equiv.), CH_3CN–CH_2Cl_2–H_2O (9 : 1 : 1), 25 °C, 8 h, 85%. AIBN = 2,2′-azobis(2-methylpropionitrile), TFA = trifluoroacetic acid.

enolate of **5** with known primary iodide **6**[4] (LDA, 75%) followed by a second alkylation with commercially available allylic bromide **7** (LDA, 87%), gave dialkylated ketone **8**. Reduction of the ketone group followed by treatment with acid gave enone **9** (DIBAL-H; then HCl, 92%), which was oxidized (IBX, MPO)[5] to the bis-enone **10** *via* the corresponding TMS enol ether (LDA, TMSCl) in 77% overall yield. Oxidative removal of the PMB protecting group with DDQ followed by oxidation of the primary alcohol with the Dess–Martin reagent gave aldehyde **11** in excellent overall yield (90% over two steps), setting the stage for the Stetter reaction.[6] This transformation was attempted using a number of carbene catalysts,[7] with the triazole-based precursor **12**[7a] giving the best results, furnishing diketone **13** in 64% yield as a single diastereoisomer.

The completion of the cage-like portion of platensimycin (**1**) from diketone **13** is shown in Scheme 2. The success of this sequence hinged on the ability to differentiate the two ketone groups. The enone of **13** could be protected selectively as the dithioacetal **14** by exposure to ethanedithiol and $BF_3{\cdot}OEt_2$ in the presence of methanol. Oxidation of the free ketone to the enone required for the radical addition step was again accomplished by treatment of the TMS enol ether (TMSOTf, Et_3N) with the IBX–MPO system.[5] The final carbon–carbon bond of the cage motif was then formed by treatment of vinylic bromide **15** with tri-*n*-butyltin hydride and AIBN in refluxing benzene, generating the tricyclic intermediate **16** in 86% yield. Reduction of the ketone to give the secondary alcohol required for the etherification was problematic, with most conditions favoring the undesired diastereoisomer **17**;‡ however, treatment of **16** with L-Selectride® in THF at −20 °C gave the secondary alcohol as a 1 : 1 mixture of **17** and **18**, the desired diastereomer, in 91% yield.§ The overall efficiency of this process could be improved by the efficient recycling of **17** to **16** upon treatment with DMP (99%). Treatment of **18** with TFA effected ring-closure to form the complete cage system, with final deprotection of the enone thioketal under oxidative conditions (DMP, 85%) giving **2** and completing the formal synthesis of (±)-platensimycin [(±)-**1**].

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‡ For example, treatment of **16** with $NaBH_4$ in THF—MeOH gave **17** in 95% yield and approximately 10 : 1 diastereoselectivity.
§ Similar results were obtained using $LiAlH(Ot\text{-}Bu_3)$.

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