Natural Products

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A Chiral Pool Based Synthesis of Platensimycin**

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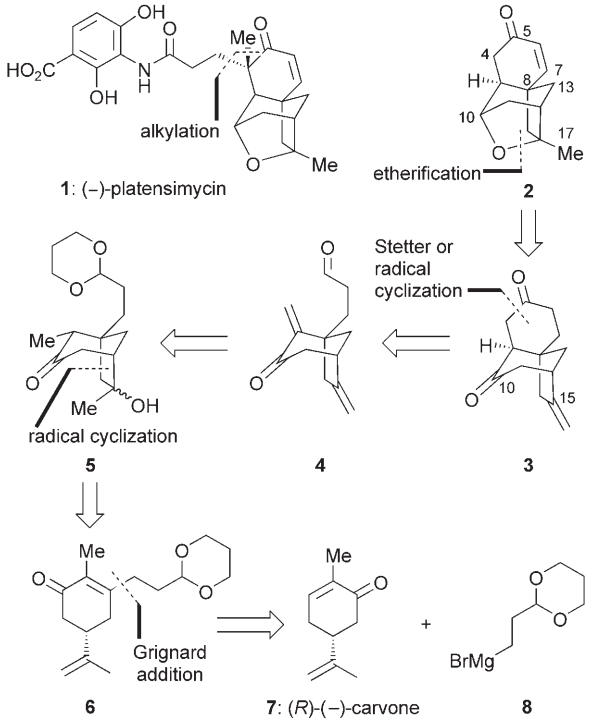
The fight against infectious disease rages on as scientists continue their struggle to overcome the emergence of drug resistance through new discoveries in chemistry and biology.[1] The recent discovery of platensimycin (**1**, Scheme 1) by a Merck research team is a beautiful illustration of how natural products chemistry combined with modern biological techniques can lead to important developments in the search for new antibiotics.[2] Platensimycin (**1**) was identified by high-throughput screening and RNA silencing technologies as a potent and selective inhibitor of the β-ketoacyl-(acyl-carrier-protein) synthase (FabF). Flexible synthetic routes to platensimycin may be particularly useful in accessing novel analogues that may prove superior to the natural product with regard to its pharmacological properties.[3] Herein we report a new synthetic strategy that leads from the readily available and inexpensive (*R*)-(−)-carvone (**7**) to the tetracyclic enone **2**—a convenient precursor to platensimycin (**1**).

Scheme 1 outlines, in retrosynthetic format, the overall plan for the construction of the required enone **2** starting from (*R*)-(−)-carvone (**7**). Thus, enone **2** was expected to arise from tricyclic ketone **3**, whose connection to bicyclic keto aldehyde **4** could be recognized through a retro-anionic or radical 1,4-addition reaction. The origins of **4** were then traced to hydroxy keto acetal **5** by standard functional-group manipulations. Finally, **5** was envisioned to arise from enone **6** through a radical-based ring closure, with the latter intermediate being readily traced back to (*R*)-(−)-carvone (**7**) through a retro-Grignard reaction.



Scheme 1. Structure and retrosynthetic analysis of (−)-platensimycin (**1**).

According to the synthetic blueprint, the synthesis of **2** began from (*R*)-(−)-carvone (**7**, Scheme 2). Thus, 1,2-addition of Grignard reagent **8** to (−)-carvone (**7**) under Luche conditions ($CeCl_3$)[4] led to the corresponding tertiary alcohol, which was directly oxidized (PCC) without further purification to afford enone **6** in 90% yield for the two steps. Intramolecular radical cyclization within the substituted carvone **6** with concomitant construction of the C8 quaternary center was accomplished through application of the sequential oxymercuration/reductive-alkylation methodology pioneered by Giese.[5] In this instance, treatment of **6** with $Hg(OAc)_2$ resulted in selective Markovnikov oxymercuration of the geminal disubstituted alkene. The intermediate organomercurial species was then reduced with $NaBH_4$, presumably leading to the corresponding primary radical, which underwent 1,4-addition onto the enone system, thereby furnishing a mixture (ca. 1:1) of *exo* (**5a**) and *endo* (**5b**, existing predominantly as its hemiketal form **5b′**; **5b′**/**5b** ca. 6:1) alcohols in 61% yield. Dehydration of a mixture of **5a**+**5b**/**5b′** with Martin's sulfurane[6a,b] led to exocyclic alkene **9**,[6c] which was subjected to a regioselective silyl enol ether formation (TMSI, HMDS) followed by an electrophilic quench with PhSeCl, and subsequent oxidative elimination (H_2O_2) to give enone **10** in 36% yield from **5a**+**5b**/**5b′**. Finally, unveiling of the dioxane-masked aldehyde in **10** was achieved under micro-

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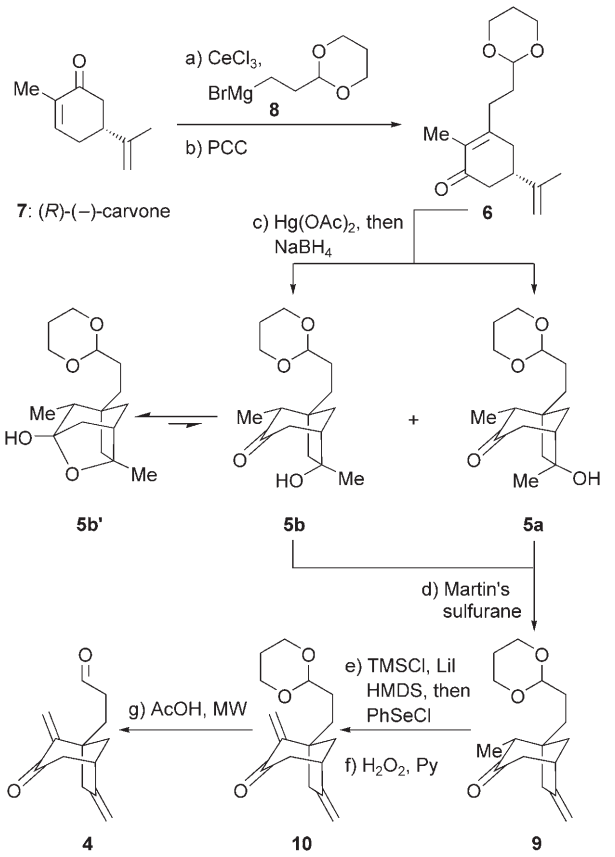
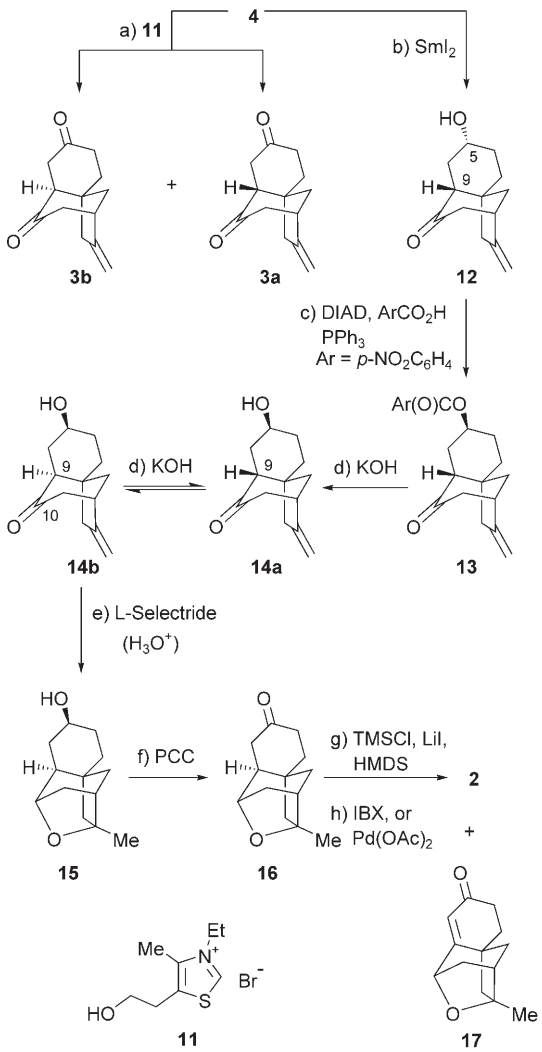


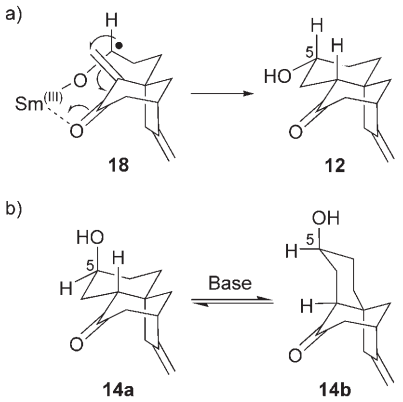
Scheme 2. Synthesis of dienone aldehyde **4**. Reagents and conditions: a) $CeCl_3$ (1.1 equiv), THF, 1 h; then **8** (1.0 equiv), 0→23 °C, 3 h; b) PCC (2.2 equiv), silica gel, CH_2Cl_2, 2 h, 90% for the two steps; c) $Hg(OAc)_2$ (1.1 equiv), THF/H_2O (1:1), 23 °C, 30 min, $NaBH_4$ (0.8 equiv), 20 °C, 45 min, **5a**: 31%, **5b**/**5b′**: 30%, **6**: 20%; d) Martin's sulfurane (1.1 equiv), CH_2Cl_2, 23 °C, 12 h; e) LiI (2.5 equiv), TMSCl (2.5 equiv), HMDS (5.0 equiv), CH_2Cl_2, −35→23 °C, 3 h; then PhSeCl (1.15 equiv), CH_2Cl_2, −78 °C, 30 min, 42% for the two steps; f) 30% aq H_2O_2 (10.0 equiv), Py (2.5 equiv), CH_2Cl_2, 0 °C, 1.5 h, 85%; g) AcOH/H_2O (5:1), 80 °C, microwave, 65 min, 85%. PCC = pyridinium chlorochromate; TMS = trimethylsilyl; HMDS = hexamethyldisilazane; Py = pyridine.



Scheme 3. Synthesis of tetracyclic enone **2**. Reagents and conditions: a) **11** (0.2 equiv), Et_3N (1.2 equiv), EtOH, 80 °C, 18 h, 65% (**3a**/**3b** ca. 5:1); b) SmI_2 (0.1 M in THF, 2.2 equiv), MeOH (2.5 equiv), 23 °C, THF (0.032 M), 2 min, 57%; c) *p*-nitrobenzoic acid (1.5 equiv), PPh_3 (1.5 equiv), DIAD (3.4 equiv), benzene, 23 °C, 2 h, 67%; d) KOH (10% in MeOH), 50 °C, 5 h, **14a**: 46%, **14b**: 45%; e) L-selectride (1.0 M in THF, 4.0 equiv), THF, −78→23 °C, 2 h; then 1 N aq HCl, 0→23 °C, 2 h, 80%; f) PCC (2.0 equiv), CH_2Cl_2, 23 °C, 1.5 h, 95%; g) TMSCl (3.3 equiv), LiI (3.3 equiv), HMDS (5.0 equiv), CH_2Cl_2, 0 °C, 3 h; h) 1. IBX (1.5 equiv), MPO (1.5 equiv), DMSO, 23 °C, 2 h, **2**: 53%, **17**: 26%; or 2. $Pd(OAc)_2$ (1.0 equiv), CH_3CN, 23 °C, 5 h, **2**: 60%, **17**: 30%; DIAD = diisopropyl azodicarboxylate; IBX = *o*-iodoxybenzoic acid; MPO = 4-methoxypyridine-*N*-oxide.

wave-irradiation conditions in AcOH/H_2O (5:1) at 80 °C to furnish dienone aldehyde **4** in 85% yield.

The next objective was the forging of the final carbocyclic ring within the tetracyclic skeleton of **2**. For the accomplishment of this goal, an intramolecular Stetter reaction[3d,7] and a SmI_2-mediated[3a,8] radical cyclization were the available options. Thus, a Stetter reaction of aldehyde **4** catalyzed by thiazolium salt **11**[7] in an ethanolic solution containing Et_3N yielded an inseparable mixture of C9 epimeric diketones **3a** and **3b** in 65% combined yield (**3a**/**3b** ca. 5:1; scheme 3). Interestingly, however, treatment of **4** with SmI_2 in THF/MeOH at room temperature resulted in the formation of hydroxy ketone **12** possessing the undesired C9 configuration as a single stereoisomer in 57% yield. A chelated transition state (**18**, Scheme 4a) is postulated as a plausible explanation for this highly stereoselective process. Accessing greater quantities of the desired C9 stereoisomer was realized through a base-mediated (KOH) equilibration process. While diketone **3a** proved unstable and hydroxy ketone **12** appeared resistant to epimerization under the basic conditions employed (KOH/MeOH), ester ketone **13**, obtained through Mitsunobu inversion of the C5 hydroxy group (*p*-$NO_2C_6H_4CO_2H$/DIAD/PPh_3, 67% yield) within **12**, underwent smooth and facile equilibration in the presence of KOH with concomitant *p*-nitrobenzoate ester hydrolysis, to afford a readily separable mixture of C9 epimers (**14a**/**14b** ca. 1.1:1, 91% yield). As seen in Scheme 4, this substrate-dependent epimerization could be rationalized by the apparent slight preference for the equatorially oriented C5 hydroxy group,



Scheme 4. a) Postulated samarium-templated ring closure of radical **18** to form hydroxy ketone **12**; and b) base-mediated equilibration of of hydroxy ketones **14a** and **14b**.

hence the reluctance of hydroxy ketone **12** to undergo the similar equilibration process (see Scheme 4b). In preparation for the casting of the remaining tetrahydrofuran system, stereoselective reduction of the C10 ketone within **14b** was carried out with L-selectride, which resulted, upon acidic workup (1N aq HCl), in the formation of the desired cage hydroxy compound **15**, in 80% yield. Sequential oxidation of the latter intermediate with PCC, followed by IBX[9] or Saegusa[10] oxidation of the silyl enol ether of **16** (TMSCl, LiI, HMDS; then IBX or $Pd(OAc)_2$), furnished a readily separable mixture of enone **2** and its regioisomer **17** (IBX: 79% overall yield, **2**/**17** ca. 2:1; $Pd(OAc)_2$: 90% overall yield, **2**/**17** ca. 2:1).[11] The recycling of **17** by conversion into **2** has been demonstrated,[3f,g] as has the conversion of **2** into **1**.[3a–c] Enone **2** exhibited identical physical properties (^1H and ^{13}C NMR spectra, $[\alpha]_D$ values, and mass spectra) to those reported previously.[3]

In conclusion, an efficient and stereocontrolled synthesis of the advanced intermediate **2** en route to (−)-platensimycin (**1**) has been accomplished by using (*R*)-(−)-carvone as an inexpensive chiral starting material. This expedient and flexible entry, which is applicable to both enantiomers of platensimycin, should offer opportunities for the synthesis of designed platensimycin analogues for chemical biology investigations.[12]

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