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A Carbonyl Ylide Cycloaddition Approach to Platensimycin**

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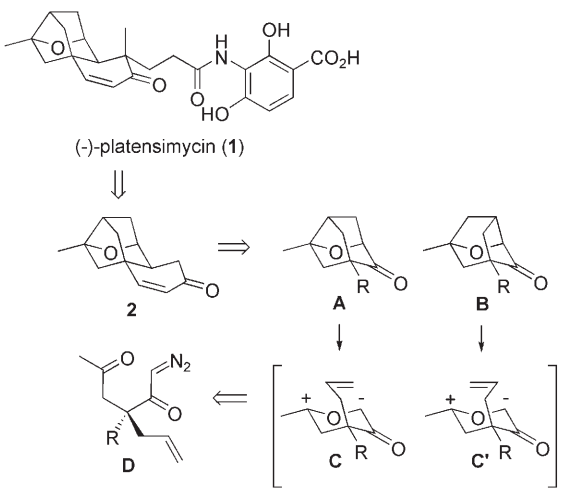
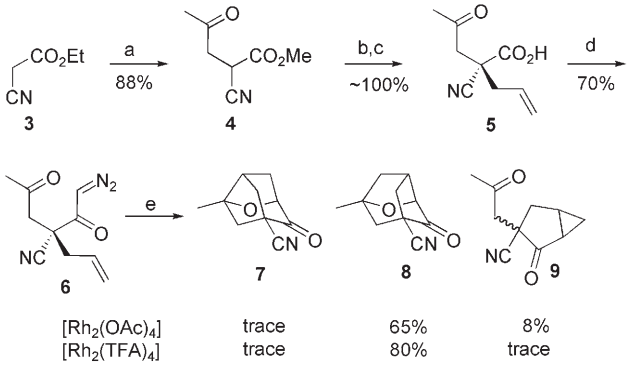
Platensimycin (**1**) is a novel broad-spectrum antibiotic (against Gram-positive bacteria) which was isolated from *Streptomyces platensis* by scientists from Merck: it inhibits bacterial growth by selectively inhibiting the condensing enzyme FabF of the bacterial fatty acid synthesis pathway.[1] Platensimycin (**1**) shows no cross-resistance to methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate *S. aureus*, and vancomycin-resistant enterococci. As a result of its remarkable biological profile and challenging structure, platensimycin (**1**) has been the focus of intense synthetic activity,[2] and herein we describe the results of our recent efforts towards the synthesis of this intriguing compound.

At the outset, a synthesis of the pivotal tetracyclic intermediate **2** from the cagelike ketone **A** was envisioned (Scheme 1). Rhodium(II)-catalyzed decomposition of α diazoketone **D** would lead to the formation of **A** and/or **B** through [3+2] cycloaddition[3] of the corresponding carbonyl ylide with conformations **C** and/or **C′**. This type of cycloaddition in the presence of rhodium(II) acetate is known to favor the formation of **B** (R = H; **A**/**B**/cyclopropanes = 6:41:36),[4] and a reversal of this product distribution seemed necessary to ensure the success of our synthetic approach.



Scheme 1. Retrosynthetic analysis of platensimycin (**1**).

In practice, preparation of the quaternary-substituted diazoketone **D** was problematic.[5] After considerable experimentation, we found that the reaction sequence was successful with R = CN. Thus, diazoketone **6** was prepared from ethyl cyanoacetate (**3**) in a straightforward manner by sequential alkylation (Scheme 2). In the presence of rhodium(II) acetate, decomposition of diazoketone **6** proceeded smoothly to yield the cagelike ketone **8**, accompanied by only a trace amount of the desired product **7**, and a small amount of cyclopropane products **9**. The use of rhodium(II) trifluoroacetate led to a clean conversion of **6** into **8**.



Scheme 2. Prototype carbonyl ylide [3+2] cycloaddition. a) NaOMe, $MeCOCH_2Cl$, MeOH; b) NaH, CH_2CHCH_2Br, THF; c) 1 N KOH, MeOH; d) $ClCO_2iBu$, TEA, diethyl ether, 0 °C; then CH_2N_2, diethyl ether, 0 °C→RT; e) 5 mol% catalyst, CH_2Cl_2. Ac = acetyl, TEA = triethylamine, TFA = trifluoroacetate.

At first glance these results were disappointing, but we recognized that the overall cyclization–cycloaddition process was more competitive than the cyclopropanation reaction, and that the LUMO-dipole/HOMO-dipolarophile (type III) interaction[6] clearly dominated in the cycloaddition process because of the introduction of a nitrile group. The desired regioselectivity would be attained through the reversal of the olefin (dipolarophile) HOMO coefficient, for which halogen substitution emerged as an appropriate possibility. Accordingly, the halogenated substrates **10**–**13** were prepared from **4** for further regioselectivity studies.

Rhodium(II)-catalyzed decomposition of **10** led to the relatively clean production of ketone **14** (Scheme 3). Under similar conditions, the (*Z*)-bromide **11** produced a relatively complex mixture from which **15** and **16**[7] were isolated in low yields. Gratifyingly, the (*E*)-bromide **12** was converted into

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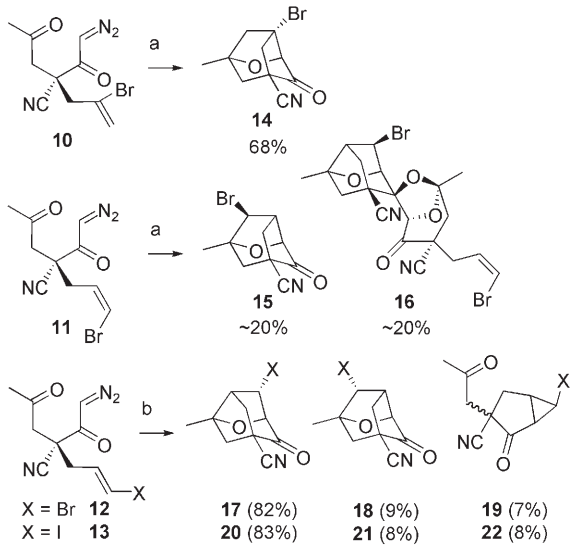
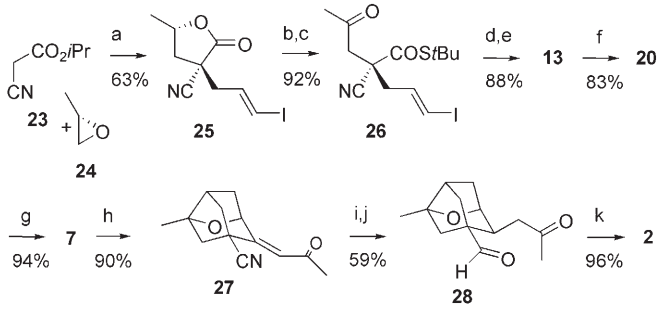


Scheme 3. Carbonyl ylide [3+2] cycloaddition of the halogenated olefins. a) 5 mol% $[Rh_2(OAc)_4]$, CH_2Cl_2; b) 3 mol% $[Rh_2(OAc)_4]$, CH_2Cl_2.

the desired ketone **17**, with only trace amounts of the alternative ketone **18** and a mixture of cyclopropanes **19**. Likewise, the (*E*)-iodide **13** gave **20** in high yield. These results affirmed the favorable reversal of the dipolarophile HOMO coefficient in the type III cycloaddition step. Steric effects may also favor the formation of **17** and **20**.

For completion of the asymmetric synthesis of platensimycin (**1**), diazoketones **12** or **13** needed to be prepared in high enantiomeric excess. An ideal choice would be the use of chiral phase-transfer catalysts[8] in the cyanocarboxylate allylation step (provided efficient reaction conditions were found).[9] However, an alternative and practical approach started with treatment of isopropyl cyanoacetate (**23**) with (*S*)-propylene oxide (**24**, 99% *ee*; Scheme 4). The resulting lactone[10] was allowed to react with (*E*)-iodoallyl iodide to give the desired lactone nitrile **25** in 63% yield, after



Scheme 4. Asymmetric synthesis of tetracycle **2**. a) **24**, NaH, THF, reflux; then (*E*)-$CHICHCH_2I$; b) *t*BuSH, Me_3Al, CH_2Cl_2, 0°C; c) DMP, CH_2Cl_2, 0°C; d) 1 N KOH, MeOH; e) $ClCO_2iBu$, TEA, diethyl ether, 0°C; then CH_2N_2, diethyl ether, 0°C→RT; f) 3 mol% $[Rh_2(OAc)_4]$, CH_2Cl_2; g) H_3PO_2, 1-ethylpiperidine, Et_3B, MeOH, 0°C; h) $MeCOCH_2PO(OMe)_2$, DIPEA, LiCl, MeCN; i) Me_2PhSiH, 2 mol% $[RhCl(Ph_3P)_3]$, toluene, 60°C; then DIBAL, toluene, −40°C; AcOH/H_2O (1:1), 0°C; j) 2 N HCl, THF, 0°C; k) TsOH, toluene, reflux. DIBAL = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, DMP = Dess–Martin periodinane, Ts = *para*-toluenesulfonyl.

chromatographic separation from the epimeric product (13%). Lactone nitrile **25** was converted into the corresponding hydroxy *tert*-butyl thioester in the presence of trimethylaluminum,[11] which in turn was transformed into ketone **26** in high yield. The carboxylic acid prepared from **26** was used for the enantioselective synthesis of diazoketone **13**, which was further converted into ketone **20**.

Reduction of **20** with hypophosphite[12] afforded tricycle **7** in high yield. The subsequent conversion of **7** into tetracycle **2** was not trivial. The eventual successful sequence began with an efficient Horner–Emmons reaction[13] to afford enone **27**. Rhodium(I)-catalyzed hydrosilylation[14] of **27**, DIBAL reduction, and careful imine hydrolysis were carried out in one pot, and it was possible to obtain keto aldehyde **28** (59%) and the epimer (23%) separately after hydrolysis of the silyl enol ether. Further transformation of **28** into the key tetracyclic intermediate **2**[15] was effected under acidic conditions, which constituted a formal synthesis of platensimycin (**1**).

The approach outlined herein represents a short and facile route to platensimycin (**1**); the enantioselective synthesis of tetracycle **2** required 11 steps (20% overall yield) from isopropyl cyanoacetate (**23**). More importantly, this approach may be easily adapted for the synthesis of platensimycin analogues, which will be the focus of our future studies.

Experimental Section

General procedure for the rhodium(II)-catalyzed cycloaddition:Rhodium acetate was added to a solution of a diazoketone in CH_2Cl_2. After stirring the mixture for 10 h, it was filtered through a pad of silica gel (hexanes/EtOAc, 1:1) to remove the catalyst, and the filtrate was then concentrated in vacuo. The products were separated by flash column chromatography.

Synthesis of iodoketonitrile **20**: In the presence of 3 mol% $[Rh_2(OAc)_4]$, **13** (300 mg) was converted into **20** (228 mg, 83%) as a mixture of the keto and hydrate forms after chromatographic separation; $R_f = 0.20$ (hexanes/acetone/CH_2Cl_2, 4:1:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.43$ (s, 1H), 4.22 (s, 1H), 3.05 (d, $J =$ 7.1 Hz, 1H), 2.75 (dd, $J = 11.9$, 3.1 Hz, 1H), 2.47 (dd, $J = 13.0$, 7.1 Hz, 1H), 2.32 (d, $J = 12.0$ Hz, 1H), 2.22 (dd, $J = 13.0$, 3.2 Hz, 1H), 1.77 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 193.6$, 115.9, 89.5, 87.5, 53.7, 53.5, 51.5, 46.8, 27.5, 23.1 ppm; IR (neat): $\tilde{\nu}_{max} = 3390$, 2978, 2874, 2247, 1740, 1632, 1444, 1383, 1243, 1113, 1026, 825, 612 cm^{-1}; FABMS (relative intensity): *m*/*z* 304 ([M^++1]; 6), 289 (7), 273 (4), 219 (18), 194 (13), 176 (15), 154 (95), 136 (100), 107 (32), 90 (30), 77 (37); HRMS (FAB) calcd for $C_{10}H_{11}O_2NI$ [M^++1]: 303.9834; found: 303.9824.

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[7] The structures of **7** and **8** (as the dinitrophenylhydrazones), and **16** were confirmed by single-crystal X-ray diffraction studies. CCDC 669284 (**7**), 669285 (**8**), and 669286 (**16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[9] In preliminary studies, the use of the (*R*,*R*)-Maruoka catalyst (Ar = 3,4,5-$F_3C_6H_2$) in the iodoallylation of cyanocarboxlyate **4** (in this case, the corresponding *tert*-butyl ester was used) resulted in formation of the product in 83% yield (53% *ee*). The use of the (*S*,*S*)-Maruoka catalyst (Ar = 3,5-$(CF_3)_2C_6H_3$) resulted in formation of the enantiomeric product (74% *ee*).

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[15] The synthesized sample of **2** has identical spectroscopic properties as those reported: $[\alpha]_D^{25} = -22.8\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.0046\ \mathrm{g\,cm^{-3}}$, $CHCl_3$).

