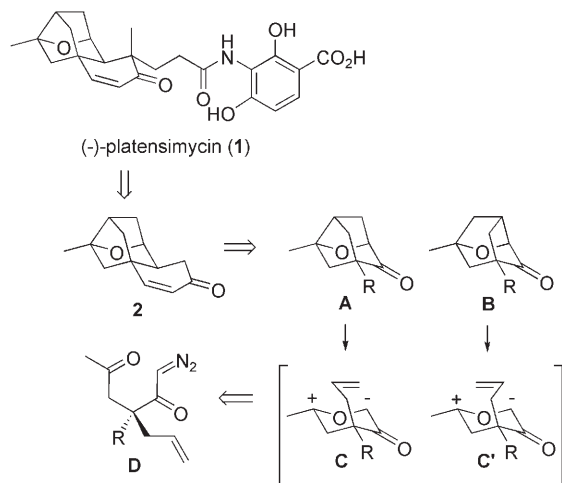


A Carbonyl Ylide Cycloaddition Approach to Platensimycin**

Chan Hyuk Kim, Ki Po Jang, Soo Young Choi, Young Keun Chung, and Eun Lee*

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 cyclo-

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

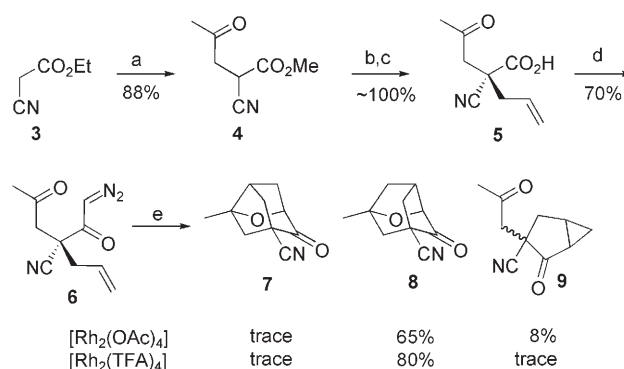
[*] C. H. Kim, K. P. Jang, S. Y. Choi, Y. K. Chung, Prof. E. Lee
Department of Chemistry, College of Natural Sciences
Seoul National University, Seoul 151-747 (Korea)
Fax: (+82) 2-889-1568
E-mail: eunlee@snu.ac.kr

[**] This work was supported by a grant from MarineBio21, Ministry of Maritime Affairs and Fisheries, Korea, and a grant from the Center for Bioactive Molecular Hybrids (Yonsei University and the Korea Science and Engineering Foundation). BK21 Graduate Fellowship grants to C.H.K. and K.P.J., and a Seoul Science Fellowship grant to C.H.K. are gratefully acknowledged. We thank Prof. Maruoka for a generous gift of his catalyst.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

addition 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.

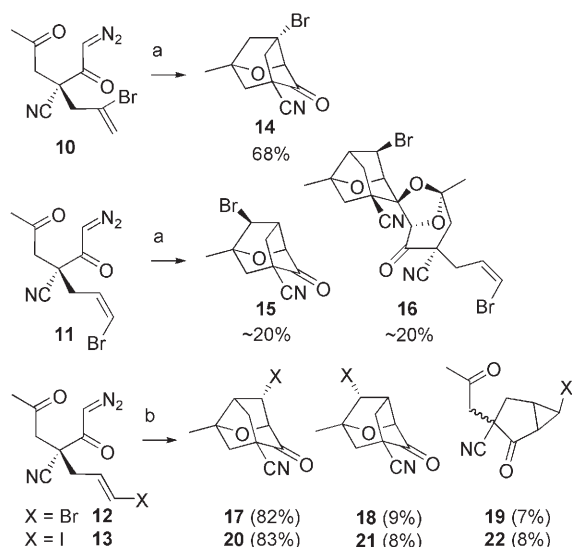
In practice, preparation of the quaternary-substituted diazoketone **D** was problematic.^[5] After considerable experimentation, we found that the reaction sequence was successful with R = CN. Thus, diazoketone **6** was prepared from ethyl cyanoacetate (**3**) in a straightforward manner by sequential 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, MeCOCH₂Cl, MeOH; b) NaH, CH₂CHCH₂Br, THF; c) 1 N KOH, MeOH; d) ClCO₂iBu, TEA, diethyl ether, 0°C; then CH₂N₂, diethyl ether, 0°C → RT; e) 5 mol % catalyst, CH₂Cl₂. 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.

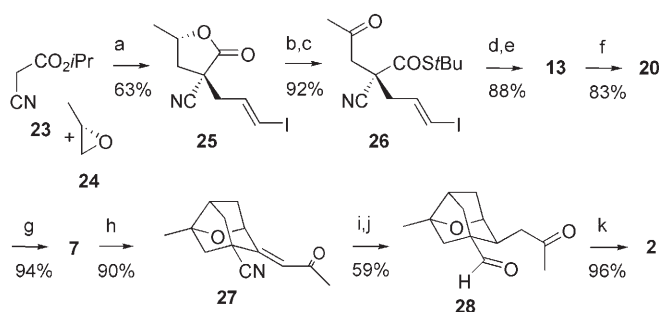
Rhodium(II)-catalyzed decomposition of **10** led to the relatively clean production of ketone **14** (Scheme 3). Under similar conditions, the (*Z*)-bromide **11** produced a relatively complex mixture from which **15** and **16**^[7] were isolated in low yields. Gratifyingly, the (*E*)-bromide **12**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



Scheme 3. Carbonyl ylide [3+2] cycloaddition of the halogenated olefins. a) 5 mol% $[\text{Rh}_2(\text{OAc})_4]$, CH_2Cl_2 ; b) 3 mol% $[\text{Rh}_2(\text{OAc})_4]$, 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*)-CHICHCH₂I; b) *t*BuSH, Me₃Al, CH₂Cl₂, 0°C; c) DMP, CH₂Cl₂, 0°C; d) 1 N KOH, MeOH; e) ClCO₂tBu, TEA, diethyl ether, 0°C; then CH₂N₂, diethyl ether, 0°C→RT; f) 3 mol% $[\text{Rh}_2(\text{OAc})_4]$, CH₂Cl₂; g) H₃PO₂, 1-ethylpiperidine, Et₃B, MeOH, 0°C; h) MeCOCH₂PO(OMe)₂, DIPEA, LiCl, MeCN; i) Me₂PhSiH, 2 mol% $[\text{RhCl}(\text{Ph}_3\text{P})_3]$, toluene, 60°C; then DIBAL, toluene, -40°C; AcOH/H₂O (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 CH₂Cl₂. 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% $[\text{Rh}_2(\text{OAc})_4]$, **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/CH₂Cl₂, 4:1:1); ¹H NMR (500 MHz, CDCl₃): δ = 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); ¹³C NMR (125 MHz, CDCl₃): δ = 193.6, 115.9, 89.5, 87.5, 53.7, 53.5, 51.5, 46.8, 27.5, 23.1 ppm; IR (neat): $\tilde{\nu}_{\text{max}}$ = 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 C₁₀H₁₁O₂NI [*M*⁺+1]: 303.9834; found: 303.9824.

Received: February 4, 2008

Published online: April 15, 2008

Keywords: antibiotics · carbonyl ylides · natural products · total synthesis

- [1] a) J. Wang, et al., *Nature* **2006**, *441*, 358–361; b) S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 11916–11920; c) S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 15547; d) H.

- Pearson, *Nature* **2006**, *441*, 260–261; e) E. D. Brown, *Nature* **2006**, *441*, 293–294; f) D. Häbich, F. von Nussbaum, *ChemMedChem* **2006**, *1*, 951–954; g) S. B. Singh, K. B. Herath, J. Wang, N. Tsou, R. G. Ball, *Tetrahedron Lett.* **2007**, *48*, 5429–5433.
- [2] For the first total synthesis, see: a) K. C. Nicolaou, A. Li, D. J. Edmonds, *Angew. Chem.* **2006**, *118*, 7244–7248; *Angew. Chem. Int. Ed.* **2006**, *45*, 7086–7090; for an asymmetric total synthesis, see: b) K. C. Nicolaou, D. J. Edmonds, A. Li, G. S. Tria, *Angew. Chem.* **2007**, *119*, 4016–4019; *Angew. Chem. Int. Ed.* **2007**, *46*, 3942–3945; for asymmetric formal syntheses, see: c) P. Li, J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 9534–9535; d) G. Lalic, E. J. Corey, *Org. Lett.* **2007**, *9*, 4921–4923; e) K. C. Nicolaou, D. Pappo, K. Y. Tsung, R. Gibe, D. Y.-K. Chen, *Angew. Chem.* **2008**, *120*, 958–960; *Angew. Chem. Int. Ed.* **2008**, *47*, 944–946; for racemic formal syntheses, see: f) Y. Zou, C.-H. Chen, C. D. Taylor, B. M. Foxman, B. B. Snider, *Org. Lett.* **2007**, *9*, 1825–1828; g) K. C. Nicolaou, Y. Tang, J. Wang, *Chem. Commun.* **2007**, 1922–1923; h) K. Tiefenbacher, J. Mulzer, *Angew. Chem.* **2007**, *119*, 8220–8221; *Angew. Chem. Int. Ed.* **2007**, *46*, 8074–8075; for syntheses of the related oxatetracyclic core of platensimycin, see: i) K. P. Kaliappan, V. Ravikumar, *Org. Lett.* **2007**, *9*, 2417–2419; j) A. K. Ghosh, K. Xi, *Org. Lett.* **2007**, *9*, 4013–4016.
- [3] For reviews on carbonyl ylide [3+2] cycloaddition, see: a) A. Padwa, *Helv. Chim. Acta* **2005**, *88*, 1357–1374; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–269.
- [4] A. Padwa, D. J. Austin, S. F. Hornbuckle, *J. Org. Chem.* **1996**, *61*, 63–71.
- [5] Diazoketone formation was sluggish when R was either vinyl, methoxymethyl, or (*N*-methoxy-*N*-methylaminocarbonyl)ethyl.
- [6] A. Padwa, G. E. Fryxell, L. Zhi, *J. Am. Chem. Soc.* **1990**, *112*, 3100–3109.
- [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.
- [8] For a recent review on chiral phase-transfer catalysis, see: T. Ooi, K. Maruoka, *Aldrichimica Acta* **2007**, *40*, 77–86; efficient catalytic asymmetric alkylation of similar α cyanocarboxylates has been reported, see: K. Nagata, D. Sano, T. Itoh, *Synlett* **2007**, 547–550.
- [9] In preliminary studies, the use of the (*R,R*)-Maruoka catalyst (Ar = 3,4,5-F₃C₆H₂) in the iodoallylation of cyanocarboxylate **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-(CF₃)₂C₆H₃) resulted in formation of the enantiomeric product (74% *ee*).
- [10] S. A. Glickman, A. C. Cope, *J. Am. Chem. Soc.* **1945**, *67*, 1012–1015.
- [11] R. P. Hatch, S. M. Weinreb, *J. Org. Chem.* **1977**, *42*, 3960–3961.
- [12] E. Lee, H. O. Han, *Tetrahedron Lett.* **2002**, *43*, 7295–7296.
- [13] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Esserfeld, S. Masamune, W. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
- [14] I. Ojima, T. Kogure, *Organometallics* **1982**, *1*, 1390–1399.
- [15] The synthesized sample of **2** has identical spectroscopic properties as those reported: $[\alpha]_{\text{D}}^{25} = -22.8 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ ($c = 0.0046 \text{ g cm}^{-3}$, CHCl₃).