Organic LETTERS

Letter

pubs.acs.org/OrgLett

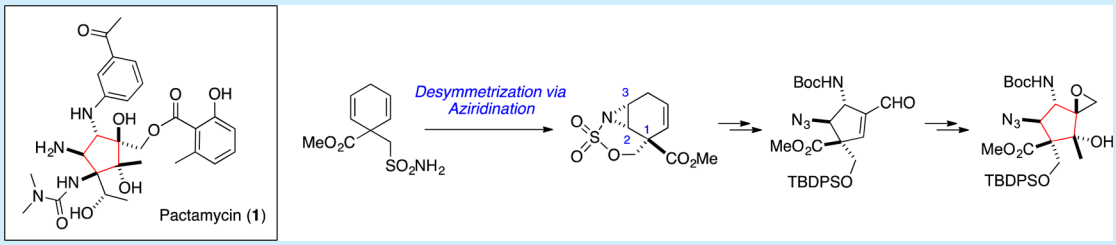
# Synthetic Study on Pactamycin: Stereoselective Synthesis of the Cyclopentane Core Framework

Atsumi Goto,[†] Satoshi Yoshimura,[†] Yuta Nakao,[†] Makoto Inai,[†] Tomohiro Asakawa,[†] Masahiro Egi,[†] Yoshitaka Hamashima,[†] Mitsuru Kondo,[‡] and Toshiyuki Kan*[,†]

[†]School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

[‡]Graduate School of Science and Technology, Shizuoka University, 836 Ohya, Suruga-ku, Shizuoka 422-8529, Japan

Supporting Information




**ABSTRACT:** The cyclopentane core framework **23** of pactamycin (**1**) was synthesized in 14 steps from symmetric cyclohexadiene **11**. Our synthetic strategy features Rh-mediated catalytic desymmetrization of **10** via aziridination and then regioselective ring-opening reaction of sulfonylaziridine **9** with $NaN_3$, ring-contraction of cyclohexene **14** by ozonolysis followed by intramolecular aldol reaction, and stereoselective construction of the sequential tetrasubstituted carbons by dihydroxylation and methylation reaction. Stereospecific incorporation of amine on tetrasubstituted carbon was achieved by Curtius rearrangement and subsequent carbamide formation.

Pactamycin (**1**), which was isolated from the fermentation broth of *Streptomyces pactum* var. *pactum* by the former Upjohn Company in 1961, exhibits antitumor, antiviral, and antiprotozoal activities as well as cytotoxicity toward Gram-positive and Gram-negative bacteria.[1−3] Structurally, pactamycin (**1**) is one of the most complex aminocyclopentitol antibiotics, featuring six contiguous stereogenic centers with three consecutive tetrasubstituted carbons on a heteroatom-rich cyclopentene core, a urea unit, and two aromatic rings (Figure 1).

During the course of our synthetic studies of biologically active natural products, we have realized that efficient syntheses of complex natural products can sometimes be achieved by utilizing latent symmetry.[4] For example, we used this strategy to accomplish an efficient total synthesis of sphingofungin E (**4**) by desymmetrization of the diene **2** via asymmetric bromolactonization and regioselective olefination of the dialdehyde derived from **3**, as shown in Scheme 1.[4b] Inspired by this result, we envisioned that aziridine derivative **9**, which is analogous to **3**, could be used to generate the sequential amino functionalities of pactamycin (**1**). Herein, we report a stereocontrolled synthesis of cyclopentane core **23** as a part of our strategy for the total synthesis of **1**.

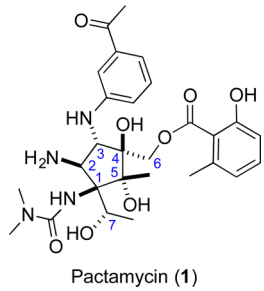
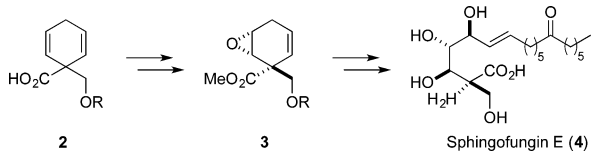



**Figure 1.** Structure of pactamycin (**1**).

**Scheme 1. Previous Synthesis of Sphingofungin E (5)**



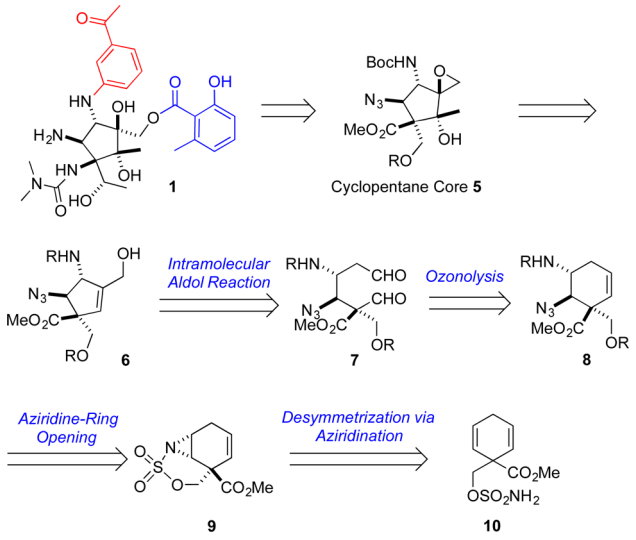

Our synthetic plan for pactamycin (**1**) is illustrated in Scheme 2. The introduction of two aromatic rings of **1** could be carried out by transition-metal-mediated aromatic amination and esterification in a late stage of the synthesis. Thus, we saw the aminocyclopentitol **5** as a key intermediate for the synthesis of **1**. Since incorporation of a urea group on tetrasubstituted carbon could be carried out by a combination of Curtius rearrangement and nucleophilic attachment of dimethylamine

**Received:** April 26, 2017




DOI: 10.1021/acs.orglett.7b01257
*Org. Lett.* XXXX, XXX, XXX−XXX

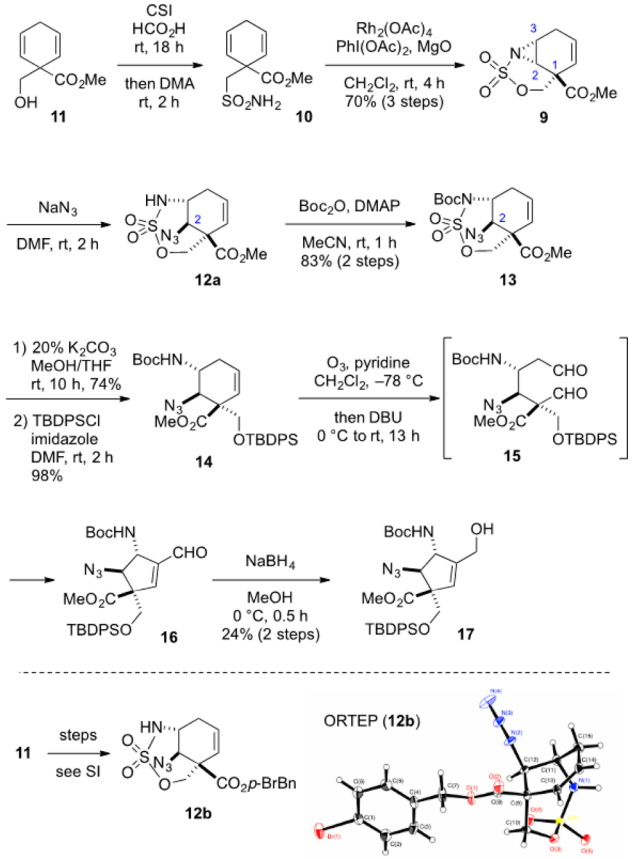
**Scheme 2. Synthetic Strategy of Pactamycin (1)**




to the isocyanate intermediate,[5] the tetra-substituted carbons of **5** would be constructed by stepwise functionalization of **6**. Although it is well-known that stereoselective functionalization of a cyclopentane ring derivative is difficult compared to that of a cyclohexane ring, we envisioned that the polyfunctional cyclopentane ring would be fixed in an appropriate conformation. Furthermore, construction of the cyclopentane ring of **2** between sterically crowded positions is expected to be difficult, so ring contraction reaction of cyclohexene **8** to cyclopentene **6** by oxidative cleavage of the double bond and intermolecular aldol reaction of dialdehyde **7** would be desirable. We envisioned that *trans*-diaminocyclohexene **8** would be synthesized from symmetric cyclohexadiene **10** by means of desymmetric aziridination and stereoselective ring opening reaction with azide.

As shown in Scheme 3, allyl alcohol **17** was synthesized from symmetric cyclohexadiene **11**, which we had used as a synthetic intermediate of sphingofungin E (**4**).[4b] Conversion from the primary alcohol **11** to the corresponding sulfamate **10** was performed by treatment with in situ generated $ClSO_2NH_2$ (derived from CSI and $HCO_2H$) in DMA. Upon treatment of **10** with a catalytic amount of $Rh_2(OAc)_4$ in the presence of $PhI(OAc)_2$, the desired aziridination proceeded smoothly to provide **9** as a single diastereomer in high yield.[6] Next, the stereospecific ring-opening reaction of aziridine **9** was carried out by treatment with $NaN_3$; nucleophilic attack occurred at the C-2 position to afford the desired azide **12a** predominantly. A similar regioselective ring-opening reaction was reported by Du Bois et al.[7] The stereochemistry of **12a** was confirmed by X-ray analysis of the *p*-bromobenzyl ester **12b** (Scheme 3).[8,9] The azide **12a** was converted to ester **14** in a three-step sequence involving protection with a Boc group, basic hydrolysis of cyclic sulfamate, and protection with a TBDPS group. Since isolation and purification of labile dialdehyde **15** were difficult, we chose to employ a one-pot ozonolysis/cyclization. In this conversion, the addition of pyridine was advantageous since reducing reagents were not required.[10] After oxidative cleavage of the double bond of **14** and in situ treatment with DBU, regioselective intramolecular aldol reaction proceeded smoothly to provide enal **16**.[11] Subsequent treatment of **16** with $NaBH_4$ resulted in smooth 1,2-reduction to provide the stable key cyclopentenol derivative **17**.

**Scheme 3. Synthesis of Cyclopentenol 17 via Ring-Contraction Reaction**



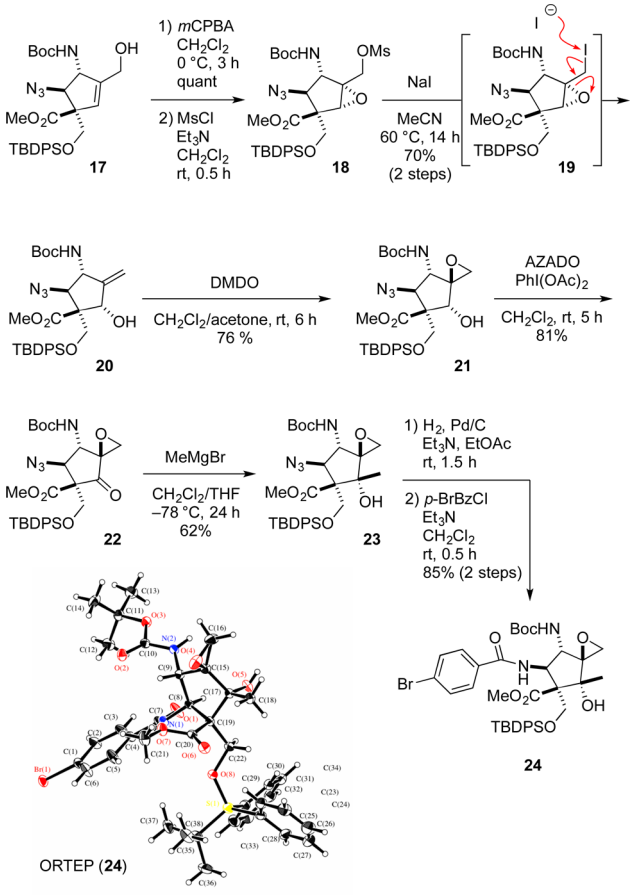

With the desired allyl alcohol **17** in hand, we next focused on stereoselective construction of the tetrasubstituted carbons at C-4 and C-5 on the cyclopentane ring, as shown in Scheme 4. Conversion of the trisubstituted double bond of **17** to the *exo*-olefin **20** was performed by epoxidation with *m*CPBA, mesylation, and treatment of **18** with a large excess of NaI in MeCN. This olefin formation reaction presumably results from $S_N2$ reaction of mesylate **18** with NaI and subsequent attack of iodonium anion on the iodoepoxide intermediate **19** to provide **20** without decomposition of the azide group. Upon treatment with DMDO, the epoxidation reaction proceeded smoothly to give *β*-epoxide **21**.[12] Conversion of **21** to cyclopentanone **22** was carried out by AZADO-mediated Iwabuchi oxidation.[13] Upon treatment of **22** with methylmagnesium bromide, alkylation proceeded smoothly to provide the *α*-alcohol **23** predominantly. Interestingly, nucleophilic attack on cyclopentane rings **20** and **22** occurred from the *β*-side exclusively. In this alkylation reaction, addition of $CH_2Cl_2$ played a key role for enhancement of the reactivity and selectivity.[14] The stereochemistry of **23** was confirmed by X-ray analysis after conversion to the corresponding *p*-bromobenzamide **24**. The stereochemistry was identical to that of **1**.[15]

As shown in Scheme 5, incorporation of the amino functionality onto the *α*-trisubstituted carbon was accomplished by Curtius rearrangement as employed in our *α*-substituted *α*-amino acid synthesis.[4] After removal of the TBDPS group, the resulting diol group of **25** was converted to methoxybenzylidene acetal. One-step incorporation of the dimethyl urea group was performed by the combination of Curtius rearrangement and addition of methylamine. After hydrolysis of the methyl

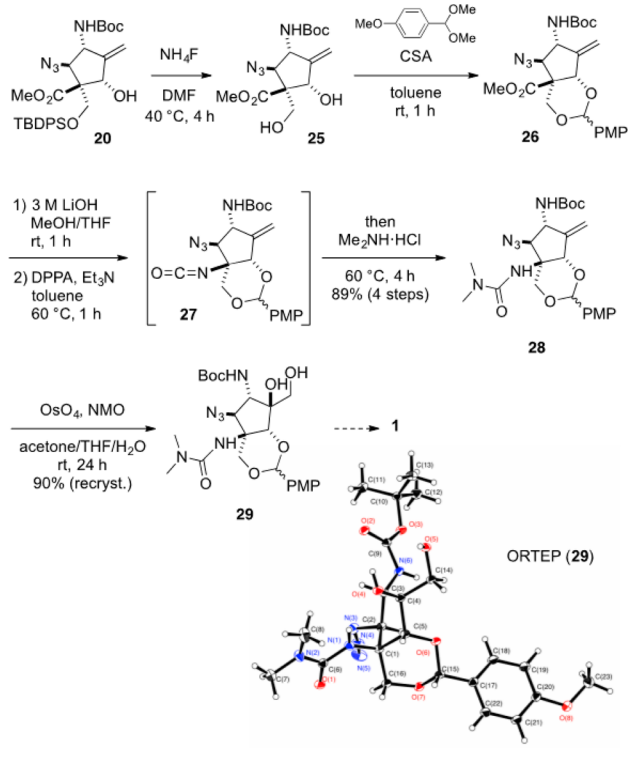


DOI: 10.1021/acs.orglett.7b01257
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 4. Stereoselective Synthesis of Cyclopentane 23**




**Scheme 5. Incorporation of Urea 28 by Curtius Rearrangement**




ester of **26** and treatment of the carboxylic acid with DPPA,[5] the desired rearrangement proceeded smoothly to afford the isocyanate intermediate **27**. In this reaction, monitoring the disappearance of carboxylic acid and subsequent addition of dimethylamine provided methyl urea **28**. Next, dihydroxylation of **28** with $OsO_4$ and NMO afforded the desired diol **29**. The oxidation reaction occurred from the convex face of **28** to provide the $\beta$-diol **29**. The stereochemistry of **29** was confirmed by X-ray crystallography analysis (see Scheme 5).[16]

In conclusion, the cyclopentane core framework **23** of pactamycin (**1**) was synthesized in 14 steps from symmetric cyclohexadiene **11**.

Our synthetic strategy features a Rh-mediated catalytic desymmetrization of **10** via aziridination followed by regioselective aziridine ring-opening reaction with $NaN_3$ and construction of the cyclopentane ring by ozonolysis followed by intermolecular aldol reaction. Subsequent stereoselective construction of three sequential tetrasubstituted carbons was accomplished by Curtius rearrangement, dihydroxylation, and methylation reaction. Further conversion of **23** and/or **29** to pactamycin (**1**) and synthesis of optically active **9** by employment of a chiral catalyst are under investigation in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01257.

Experimental details and spectroscopic data (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: kant@u-shizuoka-ken.ac.jp.

### ORCID

Toshiyuki Kan: 0000-0002-9709-6365


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was financially supported by MEXT/JSPS KAKENHI Grant Nos. JP23390007 and JP17H03973, Grants-in-Aid for Scientific Research on Priority Areas JP26102736, JP26105751, and JP16H01160 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and a Platform Project for Supporting in Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics and Structural Life Science) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

## ■ REFERENCES

(1) Isolation and biological activity of pactamycin: (a) Argoudelis, A. D.; Jahnke, H. K.; Fox, J. A. *Antimicrob. Agents Chemother.* **1962**, 191. (b) Bhuyan, B. K. *Appl. Microbiol.* **1962**, *10*, 302. (c) White, F. R. *Cancer Chemother. Rep.* **1962**, *24*, 75. (d) Taber, R.; Rekosh, D.; Baltimore, D. J. *Virol.* **1971**, *8*, 395. (e) Duchamp, D. J. *American Crystallographic Association Winter Meeting*; Albuquerque, NM, 1972; p 23. (f) Otoguro, K.; Iwatsuki, M.; Ishiyama, A.; Namatame, M.; Nishihara- Tukashima, A.; Shibahara, S.; Kondo, S.; Yamada, H.; Omura, S. *J. Antibiot.* **2010**, *63*, 381.



DOI: 10.1021/acs.orglett.7b01257
*Org. Lett.* XXXX, XXX, XXX−XXX

(2) Synthetic studies on pactamycin: (a) Tsujimoto, T.; Nishikawa, T.; Urabe, D.; Isobe, M. *Synlett* **2005**, *3*, 433. (b) Matsumoto, N.; Tsujimoto, T.; Nakazaki, A.; Isobe, M.; Nishikawa, T. *RSC Adv.* **2012**, *2*, 9448. (c) Knapp, S.; Yu, Y. *Org. Lett.* **2007**, *9*, 1359. (d) Haussener, T. J.; Looper, R. E. *Org. Lett.* **2012**, *14*, 3632. (e) Loertscher, B. M.; Young, P. R.; Evans, P. R.; Castle, S. L. *Org. Lett.* **2013**, *15*, 1930. (f) Yamaguchi, M.; Hayashi, M.; Hamada, Y.; Nemoto, T. *Org. Lett.* **2016**, *18*, 2347. Synthetic studies on jogyamycin: (g) Gerstner, N. C.; Adams, C. S.; Grigg, R. D.; Tretbar, M.; Rigoli, J. W.; Schomaker, J. M. *Org. Lett.* **2016**, *18*, 284.

(3) Total synthesis of pactamycin: (a) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschenes-Simard, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 3497. (b) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschênes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458. (c) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180. (d) Malinowski, J. T.; McCarver, S. J.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 2878. (e) Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 17990.

(4) (a) Hirooka, Y.; Ikeuchi, K.; Kawamoto, Y.; Akao, Y.; Furuta, T.; Asakawa, T.; Inai, M.; Wakimoto, T.; Fukuyama, T.; Kan, T. *Org. Lett.* **2014**, *16*, 1646. (b) Ikeuchi, K.; Hayashi, M.; Yamamoto, T.; Inai, M.; Asakawa, T.; Hamashima, Y.; Kan, T. *Eur. J. Org. Chem.* **2013**, *2013*, 6789. (c) Kan, T.; Ieda, S.; Masuda, A.; Kariyama, M.; Wakimoto, T.; Asakawa, T.; Fukuyama, T. *Heterocycles* **2012**, *86*, 1071.

(5) (a) Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(6) (a) Wehn, P. M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3802. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (c) Okada, M.; Iwashita, S.; Koizumi, N. *Tetrahedron Lett.* **2000**, *41*, 7047.

(7) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331.

(8) Detailed synthetic procedures and spectral data of **12b** are provided in the Supporting Information.

(9) CCDC-1537184 contains the supplementary crystallographic data for **12b**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

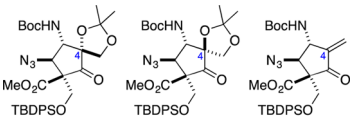
(10) Willand-Charnley, R.; Fisher, T. J.; Johnson, B. M.; Dussault, P. H. *Org. Lett.* **2012**, *14*, 2242.

(11) Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 6809.

(12) Oxidation of **20** with *m*-CPBA gave the epoxide **21** as a 1:1 mixture of the diastereomers. The stereochemistry of *β*-epoxide **21** was confirmed by X-ray crystallographic analysis of **28** (see Scheme 4).

(13) (a) Iwabuchi, Y. *Chem. Pharm. Bull.* **2013**, *61*, 1197. (b) Shibuya, M.; Sasano, Y.; Tomizawa, M.; Hamada, T.; Kozawa, M.; Nagahama, N.; Iwabuchi, Y. *Synthesis* **2011**, *2011*, 3418.

(14) The functionality of C-4 played a key role in the alkylation of ketone **22**. Although reaction of the ketone **30** with methylmagnesium bromide proceeded, **31** and **32** did not react.




(15) CCDC-1537185 contains the supplementary crystallographic data for **24**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) CCDC-1537186 contains the supplementary crystallographic data for **28**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



DOI: 10.1021/acs.orglett.7b01257
*Org. Lett.* XXXX, XXX, XXX−XXX