Natural Product

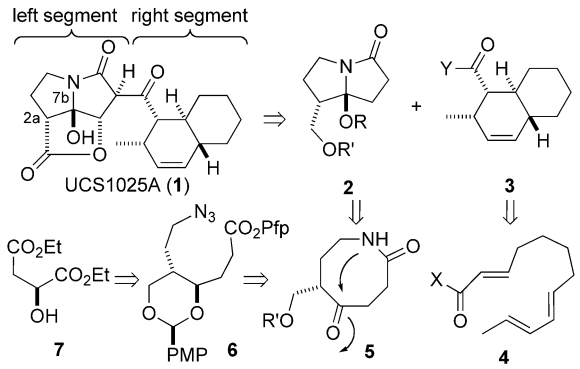
DOI: 10.1002/anie.201207800

Stereocontrolled Total Synthesis of (+)-UCS1025A**

*Kenji Uchida, Takahiro Ogawa, Yoshinori Yasuda, Hiraku Mimura, Teppei Fujimoto, Tohru Fukuyama, Toshiyuki Wakimoto, Tomohiro Asakawa, Yoshitaka Hamashima, and Toshiyuki Kan**

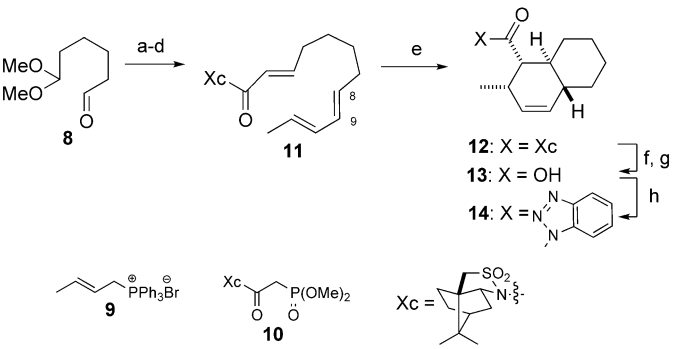
UCS1025A (**1**), an antitumor antibiotic alkaloid isolated from *Acremonium* sp. KY4917 by Yamashita et al. in 2000,[1] was shown to inhibit telomerase and have antimicrobial activity.[2] This remarkable biological activity coupled with its highly complex structure makes **1** an attractive target for total synthesis; several synthetic studies on this family of compounds have been published.[3] Three total syntheses have been reported to date: these were by the groups of Danishefsky,[4] Hoye,[5] and Christmann.[6] A crucial step in the total synthesis of **1** is the construction of a pyrrolizidinone (azabicyclo [3.3.0] octanone) skeleton possessing a hemiaminal moiety at the ring-fusion position. Consequently, stereoselective construction of the hemiaminal moiety should be a significant task in the chemical synthesis of **1**.[7] Herein, we report a stereocontrolled total synthesis of **1**.

Scheme 1 illustrates the basis of our synthetic plan. As a detailed structure–activity relationship (SAR) study is important for drug discovery and this requires the synthesis of a diverse range of analogues, it would be advantageous if the construction of the carbon framework of **1** could be performed by condensation of **2** and **3** in a convergent manner during the later stage of the total synthesis. The *trans*-fused octahydronaphthalene skeleton of **3** could be formed by an intramolecular Diels–Alder reaction[8] of **4**, and the labile aminal moiety of **2** could be prepared by stereocontrolled transannular cyclization of **5**. Furthermore, the construction of the eight-membered lactam of **5** could be accomplished by an intramolecular Staudinger/aza-Wittig reaction with Pfp (pentafluorophenyl) ester, which is a method developed by our group.[9] The precursor **6** could be prepared from L-diethyl malate **7**, an inexpensive starting material.



Scheme 1. Structure and synthetic strategy of **1**. PMP = *para*-methoxyphenyl.

As shown in Scheme 2, the synthesis of the right segment **14** commenced from aldehyde **8**, which was readily prepared from cyclohexene.[10] The stepwise elongation of **8** was achieved by a Wittig reaction with phosphonium salt **9**, a Horner–Wadsworth–Emmons reaction with phosphonate **10**,[11] and subsequent isomerization of the double bond at the C8-C9 position by heating with PhSSPh[12] to provide triene **11**. After extensive investigation, treatment with $EtAlCl_2$ at 0 °C resulted in the construction of the *trans* decalin skeleton by the crucial intramolecular Diels–Alder reaction to afford



Scheme 2. Synthesis of the right segment **14** by an intramolecular Diels–Alder reaction: a) **9**, LHMDS, THF, 0 °C to RT (85%; *trans*/*cis* = 1:1); b) 1 M HCl, THF; c) **10**, Et_3N, LiCl, MeCN (59% in 2 steps); d) PhSSPh, THF, 65 °C (84%; *trans*/*cis* = 5:1); e) $EtAlCl_2$, CH_2Cl_2, 0 °C (80%); f) $LiAlH_4$, THF, 0 °C, (90%); g) Jones reagent, acetone, 0 °C (90%); h) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C then benzotriazole, Et_3N (85%). DMF = *N*,*N*′-dimethylformamide, LHMDS = lithium hexamethyldisilazide, THF = tetrahydrofuran.

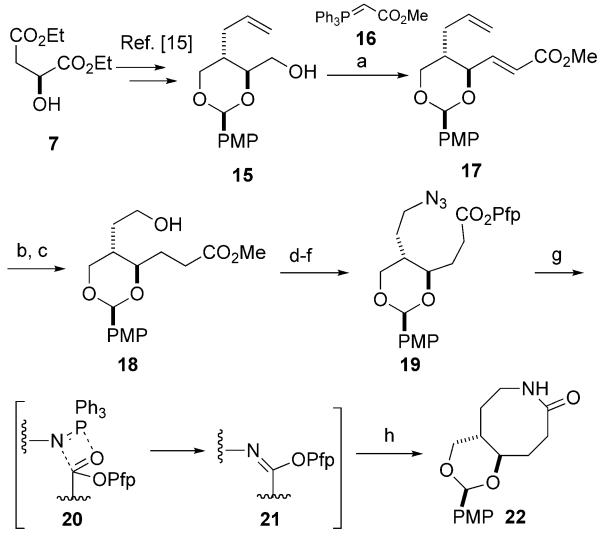
[*] Dr. K. Uchida, T. Ogawa, Y. Yasuda, Dr. T. Asakawa, Dr. Y. Hamashima, Prof. Dr. T. Kan
School of Pharmaceutical Sciences
University of Shizuoka and Global COE Program
52-1 Yada, Suruga-ku, Shizuoka 422-8526 (Japan)
E-mail: kant@u-shizuoka-ken.ac.jp
H. Mimura, Dr. T. Fujimoto, Prof. Dr. T. Fukuyama, Dr. T. Wakimoto
Graduate School of Pharmaceutical Sciences, University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

[**] The authors thank Dr. Shinji Nara and Dr. Yutaka Kanda (Kyowa Hakko Kirin Co. Ltd) for providing a natural sample of **1**. This work was financially supported by the Takeda Science Foundation, the Naito Foundation, the Uehara Memorial Foundation, the Nagase Science and Technology Foundation, MEXT/JSPS KAKENHI Grant Number 23390007, and a Grant-in-Aid for Scientific Research on Priority Areas 12045232 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207800.

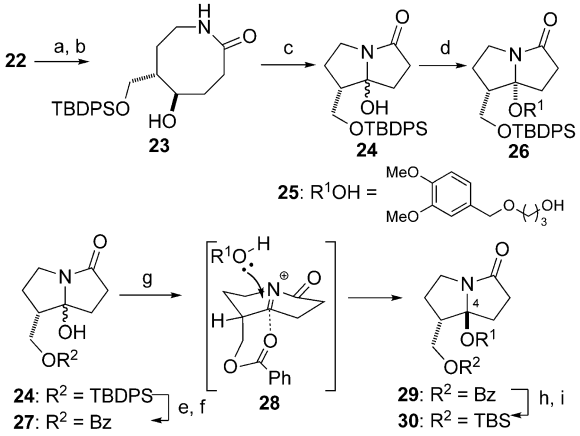
the desired bicycle **12** in 80% yield with complete diastereocontrol. Next camphorsultam **12** was converted into acylbenzotriazole **14** through a three-step sequence involving reduction to **13**,[13,14] Jones oxidation, and incorporation of benzotriazole[15] through the corresponding acid chloride.

As shown in Scheme 3, the left segment, a pyrrolizidinone skeleton, was synthesized from **15**, which was readily synthesized from commercially available L-diethyl malate **7** according to the protocol reported by Tadano and co-workers.[16] One-pot olefination of primary alcohol **15** was accomplished by IBX oxidation in the presence of ylide **16**.[17] Chemoselective ozonolysis of **17** and subsequent 1,4-reduction[18] in the presence of $NiCl_2$ with $NaBH_4$ gave alcohol **18**. After incorporation of the azide group into **18** by DPPA[19] and DBU, hydrolysis and subsequent condensation of the resultant carboxylic acid with pentafluorophenol gave ester **19**. Upon treatment of **19** with nBu$_3$P in hot toluene, the desired cyclization reaction proceeded smoothly to provide eight-membered imino ether **21** through an intramolecular Staudinger[20]/aza-Wittig reaction.[21] Hydrolysis of the isolated **21** in MeCN/H_2O under reflux afforded the desired eight-membered lactam **22** in 81% yield from **19**.[22]



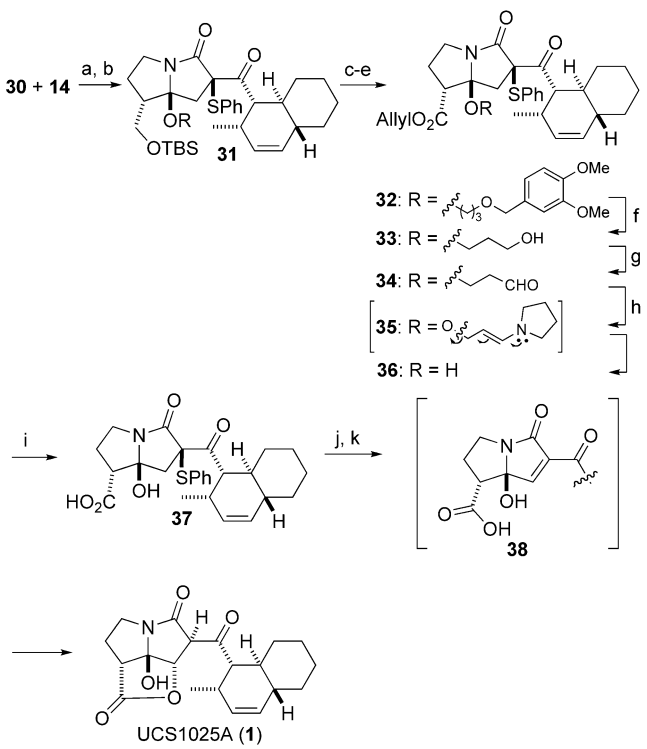
Scheme 3. Stereocontrolled synthesis of the eight-membered lactam **22**: a) **16**, IBX, CH_2Cl_2, M.S. (4Å), reflux (85%); b) O_3, CH_2Cl_2/MeOH, −78 °C then $NaBH_4$, −78 to 0 °C; c) $NaBH_4$, $NiCl_2$, MeOH, 0 °C (67% in 2 steps); d) DPPA, DBU, toluene, 80 °C (80%); e) LiOH·H_2O, THF/MeOH/H_2O; f) PfpOH, EDCI, DMAP, CH_2Cl_2 (88% in 2 steps); g) nBu$_3$P, toluene, 80 °C; h) MeCN/H_2O, reflux (81% from **19**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylamino pyridine, DPPA = diphenylphosphoryl azide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, IBX = 2-iodoxybenzoic acid, M.S. = molecular sieves, Pfp = pentafluorophenyl.

With the lactam **22** in hand, we then focused on construction of the azabicyclo[3.3.0]octanone skeleton (Scheme 4). After the removal of the benzylidene acetal of **22** under hydrogenolysis conditions and protection of the primary alcohol, TPAP-mediated oxidation of the secondary alcohol invoked a spontaneous transannular cyclization,to give bicyclic aminal **24** as a 1:1 mixture of distereoisomers. To improve the diastereoselectivity, incorporation of bulky alcohol **25**,[23] which would be readily deprotected under mild conditions, was investigated. Treatment of **24** with **25** in the presence of CSA gave **26** as a single isomer, albeit with the opposite configuration to that in **1** at the C4 hemiaminal position. Interestingly, the opposite relative configuration could be established by using substrate **27**, in which the neighboring primary alcohol is protected by a benzoyl group rather than a *tert*-butyldiphenylsilyl group. After switching the protecting group from a TBDPS to a benzoyl group, quantitatively, treatment of **27** under the similar reaction conditions gave **29** with the desired relative configuration at the C4 position. The high diastereoselectivity of this reaction suggested that the reaction proceeds via intermediate **28**, in which the acyliminium cation might interact with the carbonyl group of the benzoate[24] and the alcohol **26** would attack from the less-hindered β-face of **28**. The benzoate of **29** was changed to TBS ether to provide **30**.[25]



Scheme 4. Stereocontrolled synthesis of the left segment **30**: a) H_2, $Pd(OH)_2$/C, MeOH; b) TBDPSCl, iPr$_2$NEt, DMAP, CH_2Cl_2/iPrOH (87% in 2 steps); c) TPAP, NMO, CH_2Cl_2; d) **25**, CSA, toluene, 0 °C; e) TBAF, THF; f) Bz_2O, Et_3N, MeCN (94% in 3 steps); g) **25**, CSA, toluene, 0 °C (82%); h) LiOH·H_2O, MeOH (88%); i) TBSCl, imidazole, CH_2Cl_2 (95%). Bz = benzoyl, CSA = camphorsulfonic acid, NMO = *N*-methylmorpholine *N*-oxide, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TPAP = tetrapropylammonium perruthenate.

With the both desired segments in hand, we next focused on condensation of **14** and **30** (Scheme 5). Upon treatment of the acyl donor **14** and **30** with LHMDS, the acylation reaction produced the desired β-diketone, which contains all the carbon atoms composing the skeleton of **1**, in 96% yield. Although the obtained diketone was a mixture of stereoisomers and tautomers, a subsequent reaction with PhSCl proceeded from the convex face of the bicyclo[3.3.0]octanone skeleton to give **31** predominantly. After removal of the TBS group, 1-Me-AZADO-mediated Iwabuchi oxidation[26] directly produced the carboxylic acid. Subsequent protection with an allyl group gave **32**, which was converted into aminal **36** through a three-step sequence involving DDQ-mediated removal of the dimethoxybenzyl group,[27] DMP oxidation of the resulting alcohol **33**, and treatment of aldehyde **34** with pyrrolidine and acetic acid. The formed enamine **35** was converted into **36** by a retro-Michael-type reaction. The



Scheme 5. Completion of the total synthesis of **1**: a) LHMDS, THF, 0 °C (96%); b) NaHMDS, PhSCl, THF, 0 °C (71%); c) TBAF, AcOH, THF, RT (96%); d) 1-Me-AZADO, $PhI(OAc)_2$, CH_2Cl_2/phosphate buffer, 0 °C; e) allyl bromide, K_2CO_3, acetone, RT, (61% in 2 steps); f) DDQ, CH_2Cl_2-H_2O, RT (73%); g) DMP, CH_2Cl_2, RT; h) pyrrolidine, AcOH, CH_2Cl_2, RT (74% in 2 steps); i) $Pd(PPh_3)_4$, pyrrolidine, MeCN, RT (88%); j) DMDO, CH_2Cl_2, 0 °C; k) $CaCO_3$, toluene, 70 °C (45% in 2 steps). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMDO = dimethyldioxirane, DMP = Dess–Martin periodinane, 1-Me-AZADO = 1-methyl-azaadamantane *N*-oxyl.

dimethoxybenzyl ether protecting group was readily removed under mild reaction conditions without the decomposition of hemiaminal moiety. After deprotection of the allyl ester of **36**, DMDO-mediated oxidation of **37** gave the sulfoxide. Finally, the activated double bond of **38** was formed by the thermal β elimination of the generated sulfoxide and a subsequent intramolecular oxy-Michael reaction gave (+)-UCS1025 A (**1**); the spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS and $[\alpha]_D$) were in full agreement with those of the natural product.

In conclusion, we achieved a stereocontrolled total synthesis of (+)-UCS1025A (**1**) in a convergent manner. Our synthesis features an intramolecular Diels–Alder reaction to readily access the octahydronaphthalene skeleton of **14**, an intramolecular Staudinger-aza/Wittig reaction to give the eight-membered lactam **22**, and stereoselective construction of the labile hemiaminal moiety using the neighboring participation effect, and our novel aminal protecting group. Further modifications of the present route to prepare analogues are currently underway in our laboratories.

Received: September 27, 2012
Published online: November 9, 2012

Keywords: alkaloids · Diels-Alder reaction · hemiaminal · Staudinger/aza-Wittig reaction · total synthesis

[1] R. Nakai, H. Ogawa, A. Asai, K. Ando, T. Agatsuma, S. Matsumiya, S. Akinaga, Y. Yamashita, T. Mizukami, *J. Antibiot.* **2000**, *53*, 294 – 296.
[2] T. Agatsuma, T. Akama, S. Nara, S. Matsumiya, R. Nakai, H. Ogawa, S. Otaki, S. Ikeda, Y. Saitoh, Y. Kanda, *Org. Lett.* **2002**, *4*, 4387 – 4390.
[3] a) B. B. Snider, B. J. Neubert, *J. Org. Chem.* **2004**, *69*, 8952 – 8955; b) C. Yamauchi, M. Kuriyama, R. Shimazawa, T. Morimoto, K. Kakiuchi, R. Shirai, *Tetrahedron* **2008**, *64*, 3133 – 3140.
[4] T. H. Lambert, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 426 – 427.
[5] a) T. R. Hoye, V. Dvornikovs, *J. Am. Chem. Soc.* **2006**, *128*, 2550 – 2551; b) E. P. Sizova, "Second Generation Synthesis of UCS1025A. Synthetic Efforts Toward Total Syntheses of CJ-16,264 and Phomopsichalasin.", Ph.D. Thesis, The University of Minnesota, MN, **2009**.
[6] R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem.* **2007**, *119*, 2941 – 2944; *Angew. Chem. Int. Ed.* **2007**, *46*, 2883 – 2886.
[7] a) I. B. Seiple, S. Su, I. S. Young, C. A. Lewis, J. Yamaguchi, P. S. Baran, *Angew. Chem.* **2010**, *122*, 1113 – 1116; *Angew. Chem. Int. Ed.* **2010**, *49*, 1095 – 1098; b) A. K. Ghosh, X. Cheng, *Org. Lett.* **2011**, *13*, 4108 – 4111; c) R. Nakajima, T. Ogino, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2010**, *132*, 1236 – 1237; d) K. C. Nicolaou, D. Sarlah, T. R. Wu, W. Zhan, *Angew. Chem.* **2009**, *121*, 7002 – 7006; *Angew. Chem. Int. Ed.* **2009**, *48*, 6870 – 6874.
[8] For recent reviews on intramolecular Diels–Alder reaction see: a) K. Tadano, *Eur. J. Org. Chem.* **2009**, 4381 – 4394; b) N. Suzuki-Tanaka, T. Suzuki, T. Matsumura, Y. Hosoya, T. Nakazato, M. Nakada, *Yuki Gosei Kagaku Kyokaishi* **2011**, *69*, 646 – 660; c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem.* **2002**, *114*, 1742 – 1773; *Angew. Chem. Int. Ed.* **2002**, *41*, 1668 – 1698.
[9] a) W. Kurosawa, H. Kobayashi, T. Kan, T. Fukuyama, *Tetrahedron* **2004**, *60*, 9615 – 9628; b) W. Kurosawa, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2003**, *125*, 8112 – 8113.
[10] R. E. Claus, S. T. Schreiber, *Org. Synth. Coll. Vol. VII*, 168 – 171.
[11] Phosphonate **10** was prepared from sultam in two steps: a) NaH; $BrCH_2COBr$, toluene; b) $P(OMe)_3$, 120 °C, (84% in 2 steps); see the Supporting Information for details. For sultam: W. Oppolzer, D. Dupuis, *Tetrahedron Lett.* **1985**, *26*, 5437 – 5440.
[12] C. Moussebois, J. Dale, *J. Chem. Soc. C* **1966**, *3*, 260 – 264.
[13] The reduction to alcohol **13** allows the sultam derivatives to be readily recovered by silica gel chromatography.
[14] H. Hagiwara, K. Kobayashi, S. Miya, T. Hoshi, T. Suzuki, M. Ando, *Org. Lett.* **2001**, *3*, 251 – 254.
[15] a) A. R. Katritzky, N. Shobana, J. Pernak, A. S. Afridi, W.-Q. Fan, *Tetrahedron* **1992**, *48*, 7817 – 7822; b) A. R. Katritzky, A. Pastor, *J. Org. Chem.* **2000**, *65*, 3679 – 3682.
[16] T. Motozaki, K. Sawamura, A. Suzuki, K. Yoshida, T. Ueki, A. Ohara, R. Munakata, K. Takao, K. Tadano, *Org. Lett.* **2005**, *7*, 2261 – 2264.
[17] a) D. Crich, X. Mo, *Synlett* **1999**, 67 – 68; b) Y. Ichikawa, T. Yamaoka, K. Nakano, H. Kotsuki, *Org. Lett.* **2007**, *9*, 2989 – 2992.
[18] T. Satoh, K. Nanba, S. Suzuki, *Chem. Pharm. Bull.* **1971**, *19*, 817 – 820.
[19] a) T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203 – 6205; b) For a recent review on DPPA: T. Shioiri, *Farumashia* **2006**, *42*, 411 – 414.
[20] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635 – 646.
[21] a) Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, *48*, 1353 – 1406; b) I. Bosch, P. Romea, F. Urpi, J. Vilarrasa, *Tetrahedron Lett.* **1993**, *34*, 4671 – 4674.

[22] To construct the lactam ring of **22**, the fixation of the conformation of **19** by benzylidene acetal was essential. The reaction of a linear derivative of **22** did not provide the desired eight-membered ring.
[23] Primary alcohol **25** was prepared from 3,4-dimethoxybenzaldehyde in two steps: a) 1,3-propanediol, CSA, benzene, 80 °C; b) Diisobutylaluminium hydride, Et_2O, 0 °C (80 % in two steps); see the Supporting Information for details
[24] A similar neighboring group participation for the direction of the stereochemical outcome has been observed in the glycosylation reaction of 2-acylhexose derivatives, see: a) L. K. Mydock, A. V. Demchenko, *Org. Biomol. Chem.* **2010**, *8*, 497–510; b) T. J. Boltje, T. Buskas, G.-J. Boons, *Nat. Chem.* **2009**, *1*, 611–622.
[25] The protection group of the primary alcohol should be optimized for each conversion, because the oxidation of the benzoate derivatives of **23** caused β elimination, and the condensation of **29** with the right segment resulted in a low yield. The relative configuration was determined by nOe difference spectroscopy; see the Supporting Information.
[26] M. Shibuya, M. Tomizawa, I. Suzuki, Y. Iwabuchi, *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.
[27] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885–888.

