

Total synthesis of (+)-furanomycin

Sung Ho Kang*† and Sung Bae Lee

Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejeon 305-701, Korea

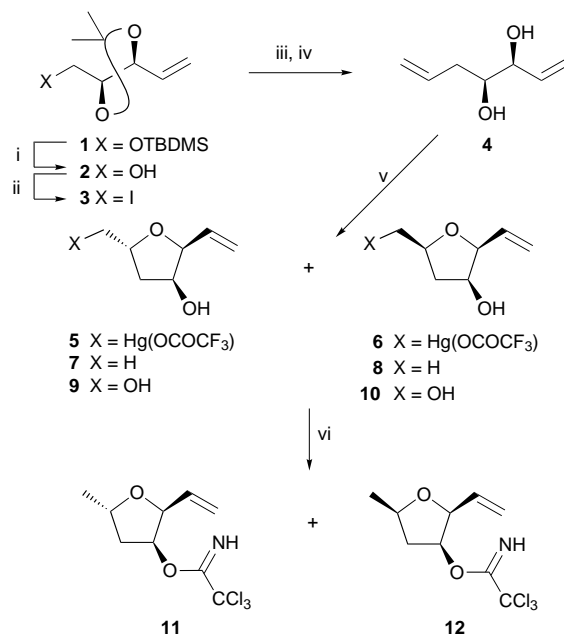
A highly enantioselective total synthesis of (+)-furanomycin **24** has been achieved *via* the mercury cation-mediated cyclizations of γ -hydroxy alkene **4** and homoallylic trichloroacetimidate **11** to install the *trans*-2,5-disubstituted tetrahydrofuran and the (α S)-amino acid side chain, respectively.

In 1967 Katagiri *et al.* discovered a novel antibiotic (+)-furanomycin from a culture filtrate of *Streptomyces threomyticus* (ATCC 15795),¹ which binds to *E. coli* isoleucyl-tRNA synthetase, to be charged to *E. coli* isoleucine tRNA and subsequently incorporated into protein.² Biosynthetically it is believed to be derived from two acetates and one propionate.³ The antibiotic also functions as a competitive antagonist of isoleucine and suppresses the growth of T-even coliphage more effectively than T-odd.¹ Originally its molecular structure was assigned as (+)-(2*R*)-2-amino-2-[(2*R*,5*R*)-2,5-dihydro-5-methyl-2-furyl]acetic acid by spectroscopic data and chemical degradation experiments,¹ but later revised as (+)-(2*S*)-2-amino-2-[(2*R*,5*S*)-2,5-dihydro-5-methyl-2-furyl]-acetic acid by X-ray crystallography⁴ and a stereodefined synthesis.⁵ Although (+)-furanomycin **24** has a seemingly simple structure, its highly enantiospecific synthesis has not been established, in part due to the difficulties in assembling the *trans*-2,5-dihydrofuran and (*S*)-amino carboxylic acid units. Here we describe a highly enantiocontrolled total synthesis of (+)-furanomycin **24** employing mercury cation-promoted cyclizations of γ -hydroxy alkene **4** and homoallylic trichloroacetimidate **11** to construct the aforementioned functionalities.

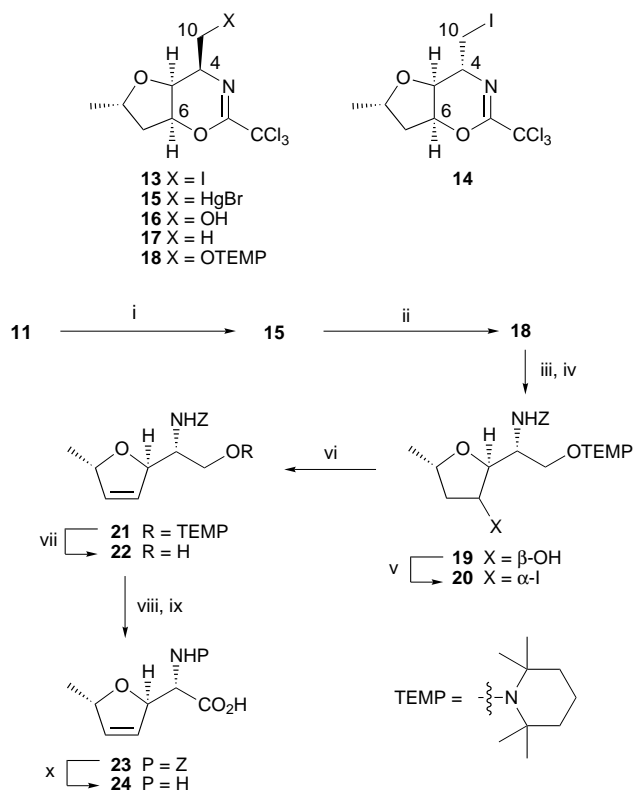
The known silyl ether **1**, prepared from dimethyl L-tartrate in 83% overall yield,⁶ was desilylated using TBAF, and the resulting alcohol **2**, [α]_D²³ -3.1 (*c* 1.01, CHCl₃), was treated with I₂, PPh₃ and imidazole in THF⁷ to yield the corresponding iodide **3**, [α]_D²² -10.1 (*c* 1.01, CHCl₃), quantitatively from **1** (Scheme 1). The substitution reaction of **3** was conducted with vinylmagnesium bromide, which should be generated freshly, in the presence of CuBr·SMe₂ and HMPA in THF at -50 °C.⁸ The somewhat volatile diene acetonide, without purification, was hydrolyzed with methanolic HCl to give diene diol **4**, [α]_D²³ -11.6 (*c* 1.01, CHCl₃), in 75% overall yield. For the stereoselective formation of *trans*-2,5-disubstituted tetrahydrofuran, the cyclization⁹ of **4** was attempted using I₂, IBr or *N*-iodosuccinimide (NIS) under various reaction conditions to provide a 1-3 : 1 mixture of *trans*- and *cis*-isomers. However, when Hg(OCOFCF₃)₂ was employed as an electrophile, the stereoselectivity was improved significantly. Accordingly, **4** was treated with Hg(OCOFCF₃)₂ in the presence of K₂CO₃ in THF at -78 °C to afford a mixture of *trans*- and *cis*-2,5-disubstituted tetrahydrofurans **5** and **6**, which was found to revert to the starting material **4** during work-up with brine or aq. KBr and chromatographic purification. In order to elude the reversion, the *in situ* demercuration of the crude organomercurials **5** and **6** was attempted with various reducing reagents¹⁰ in the absence or presence of phase transfer catalyst, NaOAc, NaOH or AcOH to furnish the expected *trans*- and *cis*-tetrahydrofurans **7** and **8**, accompanied by variable amounts of the starting diol **4** and alcohols **9** and **10**. After intensive experimentation, reproducible demercuration conditions were

established, involving treating the cyclization reaction mixture *in situ* with BEt₃ and LiBH₄ at -78 °C to produce an inseparable 8.5-9 : 1 mixture of **7**, [α]_D²² +57.0 (*c* 1.00, CHCl₃), and **8** in 83% overall yield from **4** without appreciable formation of side products.

The mixture of **7** and **8** was converted into the readily separable trichloroacetimidates **11** and **12**, which provided after chromatographic purification the requisite imidate **11**, [α]_D²² +47.0 (*c* 1.00, CHCl₃), in 83% yield. While the proposed cyclization¹¹ of **11** hardly proceeded with I₂ or NIS, the use of IBr resulted in poor stereoselectivity,¹² yielding a 2.5 : 1 mixture of iodides **13** and **14**, of which the relative stereochemistries were determined by NOE difference experiments, *i.e.* irradiation at H-C(6) showed enhancements at H-C(4) for the former and at H₂-C(10) for the latter (Scheme 2). On the other hand, when the intramolecular amination of **11** was performed with Hg(OCOFCF₃)₂ in the presence of K₂CO₃ in THF at 0 °C, only the desired organomercury bromide **15** could be isolated in higher than 95% yield after work-up with aq. KBr. Its stereochemistry was corroborated by converting it into iodide **13** with I₂ in THF. For the oxidation of **15** to alcohol **16**, oxygen was bubbled vigorously through a solution of **15** and NaBH₄ in DMF,¹³ but only the reductive demercuration product **17** was generated. Alternatively exposure of **15** to TEMPO and LiBH₄ in the presence of BEt₃ in THF provided the oxidized product **18**, mp 134.5-135.5 °C, [α]_D²³ -32.0 (*c* 0.99, CHCl₃), in 76% yield. It is noted that without BEt₃ the chemical yield decreased to 50-55%. The dihydro-1,3-oxazine heterocycle of **18** was hydrolyzed with HCl and then the unmasked amino alcohol was



Scheme 1 Reagents and conditions: i, Bu₄NF, H₂O, THF, 20 °C; ii, I₂, PPh₃, imidazole, THF, 20 °C; iii, CH₂=CHMgBr, CuBr·SMe₂, HMPA, THF, -50 °C; iv, 6 M HCl, MeOH, 20 °C; v, Hg(OCOFCF₃)₂, K₂CO₃, THF, -78 °C, then Et₃B, LiBH₄, -78 °C; vi, Cl₃CCN, DBU, MeCN, -30 °C



Scheme 2 Reagents and conditions: i, $\text{Hg}(\text{OCOFC}_3)_2$, K_2CO_3 , THF, 0 °C, then aq. KBr; ii, TEMPO, Et_3B , LiBH_4 , THF, 20 °C; iii, 6 M HCl, MeOH, THF, reflux; iv, BnOCOCl , K_2CO_3 , MeOH, 20 °C; v, I_2 , PPh_3 , DMAP, PhH, CH_2Cl_2 , 0 °C, then 60 °C; vi, DBU, DMF, 80 °C; vii, Zn, NH_4Cl , H_2O , MeOH, 80 °C; viii, $(\text{COCl})_2$, DMSO; ix, NaClO_2 , NaH_2PO_4 , 2-methylbut-2-ene, Bu^tOH , H_2O , 20 °C; x, PhSMe, TFA, 50 °C

protected with benzyl chloroformate to afford carbamate **19**, $[\alpha]_{\text{D}}^{25} -12.0$ (c 1.00, CHCl_3), in 95% overall yield.

The dihydrofuryl ring could not be formed by the basic or pyrolytic elimination reaction of the mesylate, triflate or xanthate derivatives of **19**. In addition their substitution reaction with iodide or phenylselenide anion did not yield the expected product. Various experimental attempts revealed that iodide **20**, $[\alpha]_{\text{D}}^{25} -65.2$ (c 0.99, CHCl_3) could be prepared in 76% yield by treating **19** with I_2 and PPh_3 in the presence of DMAP in a mixture of benzene and CH_2Cl_2 , while the reaction using imidazole⁷ instead of DMAP resulted in a poor chemical yield of 35%. The ensuing elimination reaction was effected by

heating **20** with DBU in DMF to provide dihydrofuran **21**, $[\alpha]_{\text{D}}^{27} +105.3$ (c 1.02, CHCl_3), regioselectively in 89% yield. The TEMP group of **21** was reductively removed with zinc dust in methanolic NH_4Cl to afford the primary alcohol **22**, $[\alpha]_{\text{D}}^{28} +195.8$ (c 0.99, CHCl_3), in 92% yield. Since Jones oxidation of **22** proceeded inefficiently, it was oxidized using Swern conditions¹⁴ followed by sodium chlorite¹⁵ to give carboxylic acid **23**, $[\alpha]_{\text{D}}^{27} +175.4$ (c 0.57, MeOH), in 89% yield. Finally removal of the BnOCO group of **23** with thioanisole in TFA produced (+)-furanomycin **24**, mp 222–224 °C, $[\alpha]_{\text{D}}^{26} +136.0$ (c 0.4, H_2O), in 97% yield, the physical and spectroscopic data of which were identical with those previously reported.

Financial support from the Korea Science and Engineering Foundation (971-0302-010-2) is gratefully acknowledged.

Notes and References

† E-mail: shkang@kaist.ac.kr

- K. Katagiri, K. Tori, Y. Kimura, T. Yoshida, T. Nagasaki and H. Minato, *J. Med. Chem.*, 1967, **10**, 1149.
- T. Kohno, D. Kohda, M. Haruk, S. Yokoyama and T. Miyazawa, *J. Biol. Chem.*, 1990, **265**, 6931.
- R. J. Parry and H. P. Buu, *J. Am. Chem. Soc.*, 1983, **105**, 7446; R. J. Parry, R. Turakhia and H. P. Buu, *J. Am. Chem. Soc.*, 1988, **110**, 4035.
- M. Shiro, H. Nakai, K. Tori, J. Nishikawa, Y. Yoshimura and K. Katagiri, *J. Chem. Soc., Chem. Commun.*, 1980, 375.
- M. M. Joullie, P. C. Wang and J. E. Semple, *J. Am. Chem. Soc.*, 1980, **102**, 887; J. E. Semple, P. C. Wang, Z. Lysenko and M. M. Joullie, *J. Am. Chem. Soc.*, 1980, **102**, 7505.
- I. Savage and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1989, 717; S. H. Kang and H.-W. Choi, *Chem. Commun.*, 1996, 1521.
- P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Chem. Commun.*, 1979, 978; P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2866; P. J. Garegg, R. Johansson, C. Ortega and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 1982, 682.
- H. O. House, C.-Y. Chu, J. M. Wilkins and M. J. Umen, *J. Org. Chem.*, 1975, **40**, 1460; E. Erdik, *Tetrahedron*, 1984, **40**, 641.
- T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309; J.-C. Harmange and B. Figadere, *Tetrahedron: Asymmetry*, 1993, **4**, 1711.
- R. P. Quirk and R. E. Lea, *J. Am. Chem. Soc.*, 1976, **98**, 5973; M. C. Benhamou, G. Etamad-Moghadam, V. Speziale and A. Lattes, *Synthesis*, 1979, 891; K. E. Harding, R. Stephens and D. R. Hollingsworth, *Tetrahedron Lett.*, 1984, **25**, 4631.
- G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321.
- A. R. Chamberlin, R. M. Mulholland, Jr., S. D. Kahn and W. J. Hehre, *J. Am. Chem. Soc.*, 1987, **109**, 672.
- C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.*, 1974, **96**, 870.
- A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
- B. S. Bal, W. E. Childers and H. W. Pinnick, *Tetrahedron*, 1981, **37**, 2091.

Received in Cambridge, UK, 27th January 1998; 8/00727F