Total synthesis of (+)-furanomycin

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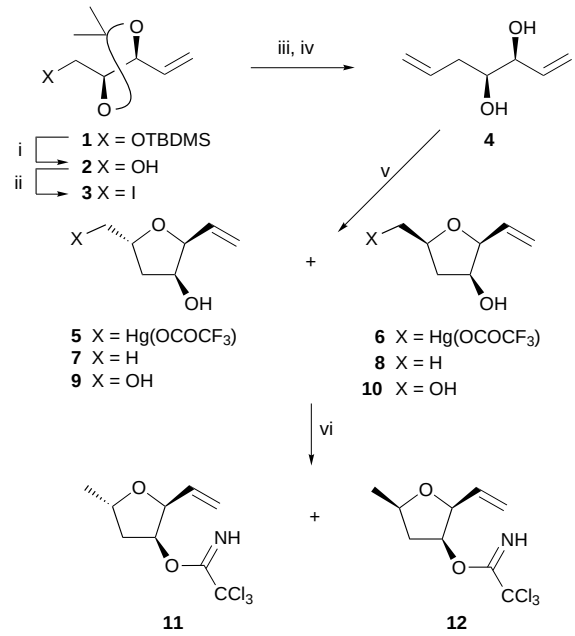
A highly enantioselective total synthesis of (+)-furanomycin 24 has been achieved *via* the mercury cation-mediated cyclizations of γ-hydroxy alkene 4 and homoallylic trichloroacetimidate 11 to install the *trans*-2,5-disubstituted tetrahydrofuran and the (α*S*)-amino acid side chain, respectively.

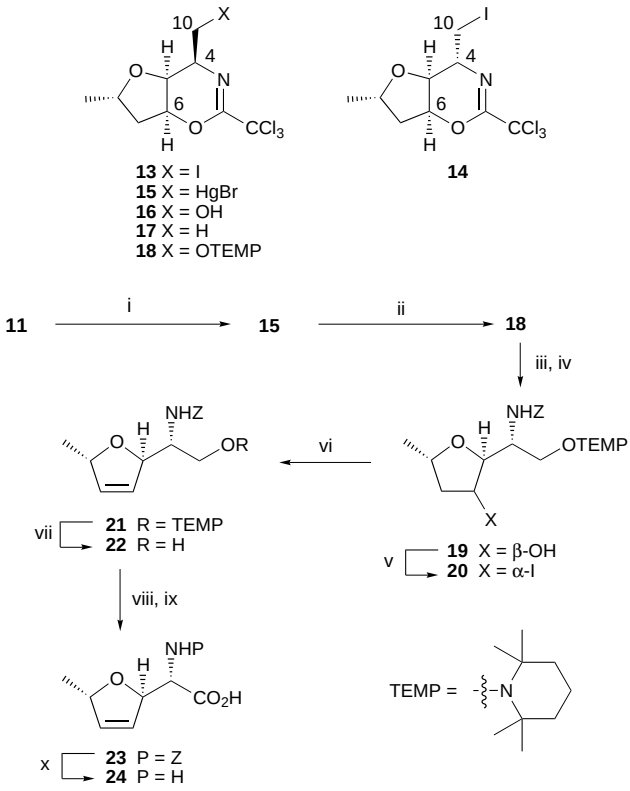
In 1967 Katagiri *et al.* discovered a novel antibiotic (+)-furanomycin from a culture filtrate of *Streptomyces threomyceticus* (ATCC 15795),[1] which binds to *E. coli* isoleucyl-tRNA synthetase, to be charged to *E. coli* isoleucine tRNA and subsequently incorporated into protein.[2] Biosynthetically it is believed to be derived from two acetetes 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 crystallography[4] 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-dihyrofuran 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**, $[\alpha]_D^{23}$ −3.1 (*c* 1.01, $CHCl_3$), was treated with I_2, PPh_3 and imidazole in THF[7] to yield the corresponding iodide **3**, $[\alpha]_D^{22}$ −10.1 (*c* 1.01, $CHCl_3$), quantitatively from **1** (Scheme 1). The substitution reaction of **3** was conducted with vinylmagnesium bromide, which should be generated freshly, in the presence of $CuBr{\cdot}SMe_2$ 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**, $[\alpha]_D^{23}$ −11.6 (*c* 1.01, $CHCl_3$), in 75% overall yield. For the stereoselective formation of *trans*-2,5-disubstituted tetrahydrofuran, the cyclization[9] of **4** was attempted using I_2, IBr or *N*-iodosuccinimide (NIS) under various reaction conditions to provide a 1–3 : 1 mixture of *trans*- and *cis*-isomers. However, when $Hg(OCOCF_3)_2$ was employed as an electrophile, the stereoselectivity was improved significantly. Accordingly, **4** was treated with $Hg(OCOCF_3)_2$ in the presence of K_2CO_3 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 reagents[10] 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 BEt_3 and $LiBH_4$ at −78 °C to produce an inseparable 8.5–9 : 1 mixture of **7**, $[\alpha]_D^{22}$ +57.0 (*c* 1.00, $CHCl_3$), 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**, $[\alpha]_D^{22}$ +47.0 (*c* 1.00, $CHCl_3$), in 83% yield. While the proposed cyclization[11] of **11** hardly proceeded with I_2 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 H_2–C(10) for the latter (Scheme 2). On the other hand, when the intramolecular amination of **11** was performed with $Hg(OCOCF_3)_2$ in the presence of K_2CO_3 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 I_2 in THF. For the oxidation of **15** to alcohol **16**, oxygen was bubbled vigorously through a solution of **15** and $NaBH_4$ in DMF,[13] but only the reductive demercuration product **17** was generated. Alternatively exposure of **15** to TEMPO and $LiBH_4$ in the presence of BEt_3 in THF provided the oxidized product **18**, mp 134.5–135.5 °C, $[\alpha]_D^{23}$ −32.0 (*c* 0.99, $CHCl_3$), in 76% yield. It is noted that without BEt_3 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, Bu_4NF, H_2O, THF, 20 °C; ii, I_2, PPh_3, imidazole, THF, 20 °C; iii, CH_2=CHMgBr, $CuBr{\cdot}SMe_2$, HMPA, THF, −50 °C; iv, 6 M HCl, MeOH, 20 °C; v, $Hg(OCOCF_3)_2$, K_2CO_3, THF, −78 °C, then Et_3B, $LiBH_4$, −78 °C; vi, Cl_3CCN, DBU, MeCN, −30 °C



Scheme 2 *Reagents and conditions*: i, $Hg(OCOCF_3)_2$, 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, $(COCl)_2$, DMSO; ix, $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, Bu^{t}OH, H_2O, 20 °C; x, PhSMe, TFA, 50 °C

protected with benzyl chloroformate to afford carbamate **19**, $[\alpha]_D^{25}$ −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**, $[\alpha]_D^{25}$ −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 imidazole[7] 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**, $[\alpha]_D^{27}$ +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**, $[\alpha]_D^{28}$ +195.8 (*c* 0.99, $CHCl_3$), in 92% yield. Since Jones oxidation of **22** proceeded inefficiently, it was oxidized using Swern conditions[14] followed by sodium chlorite[15] to give carboxylic acid **23**, $[\alpha]_D^{27}$ +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, $[\alpha]_D^{26}$ +136.0 (*c* 0.4, H_2O), in 97% yield, the physical and spectroscopic data of which were identical with those previously reported.

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Notes and References

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