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A short route to N-protected furanomycin, 5′-epi-furanomycin and isofuranomycin derivatives

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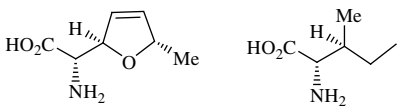
ABSTRACT

A short new route to N-protected L-(+)-furanomycin and two of its isomeric derivatives has been developed, which featured the utility of D-serine as a chiral pool material and ring-closing metathesis as a key ring-forming step.

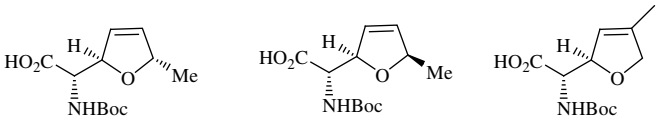
1. Introduction

L-(+)-Furanomycin **1** (Fig. 1), isolated[1] from *Streptomyces threomyceticus*, is a naturally occurring α-amino acid, which shows antibiotic activity against microorganisms such as *E. coli*, *Bacillus subtilis* and several *Salmonella*- and *Shigella* strains. Later studies[2] have revealed that furanomycin binds to *E. coli* isoleucyl-tRNA synthetase to be incorporated into a protein. The antibiotic also functions as a competitive antagonist of isoleucine and suppresses the growth of T-even coliphage more effectively than T-odd.[1] The translational ability of furanomycin is unusual since the structure of furanomycin differs considerably from that of isoleucine. However, NMR studies have indicated[2] that the enzyme-bound conformation of these two amino acids is very similar and this, in turn, has renewed interest in furanomycin and similar in compounds as possible candidates with regard to protein engineering.[3] Due to its activity, and somewhat moderate structural complexity, a number of syntheses of furanomycin[3c,4] and analogues[5] thereof have been described. However, a general route to furanomycin and its analogues, particularly those having isomeric methyl group that would allow a structure-activity study of this class of compounds, is desirable. In continuation of our interest[6] in the synthesis of heterocyclic amino acids,[7] we report herein a general route to *N*-protected furanomycin **3** (Fig. 2), 5′-epi-furanomycin **4** and isofuranomycin **5** derivatives using D-serine as a chiral pool material and ring-closing metathesis as the key step.



furanomycin **1** Isoleucine **2**

Figure 1.



3 **4** **5**

Figure 2.

2. Results and discussion

As demonstrated retrosynthetically in Figure 3, we envisioned that direct access to furanomycin **3** and its 5′-epimer **4** in their N-protected form could become available through the ring-closing metathesis of the epimeric mixture of dienes represented by structure **8**, if the epimeric mixture of products **6** and **7** becomes separable at some stage during the synthesis. The diene mixture **8** was thought to be obtainable by O-alkylation of stereoisomerically pure *syn*-allyl alcohol **9** with racemic 3-chloro-1-butene. Compound **9** could be obtained through a *syn*-selective vinylation of the known D-serine-derived Garner's aldehyde[8] **10**. Compound **9** was also thought of as an appropriate intermediate for the preparation of the isofuranomycin derivative **5** following an identical sequence of events as outlined in Figure 3 but using methallyl bromide in the O-alkylation step.

We thus focused on the preparation of the common intermediate **9** from **8**. *syn*-Selective vinylation of Garner's aldehyde has been achieved[9] in many instances with a varying degree of selectivity in favour of the desired *syn*-allyl alcohol. We took recourse in the method developed by Herold[10] for its simplicity and higher level of selectivity, and to avoid the use of procedures involving less stable vinylating agents which may prove to be less amenable for

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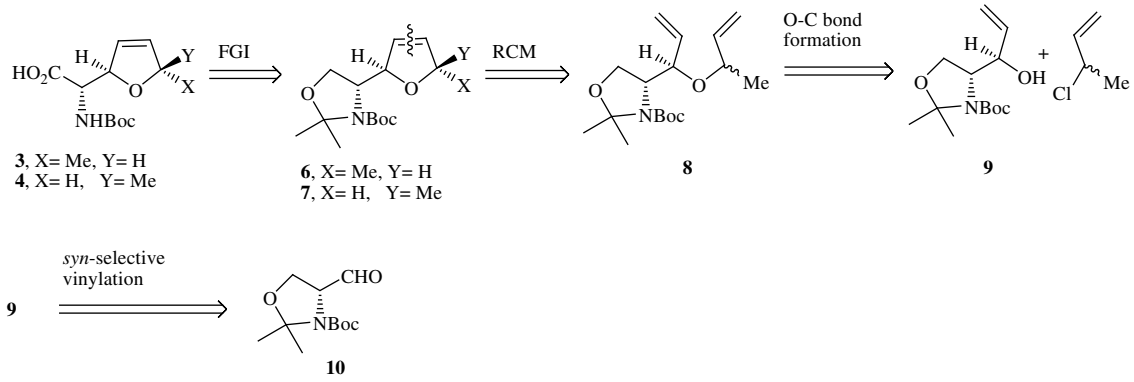
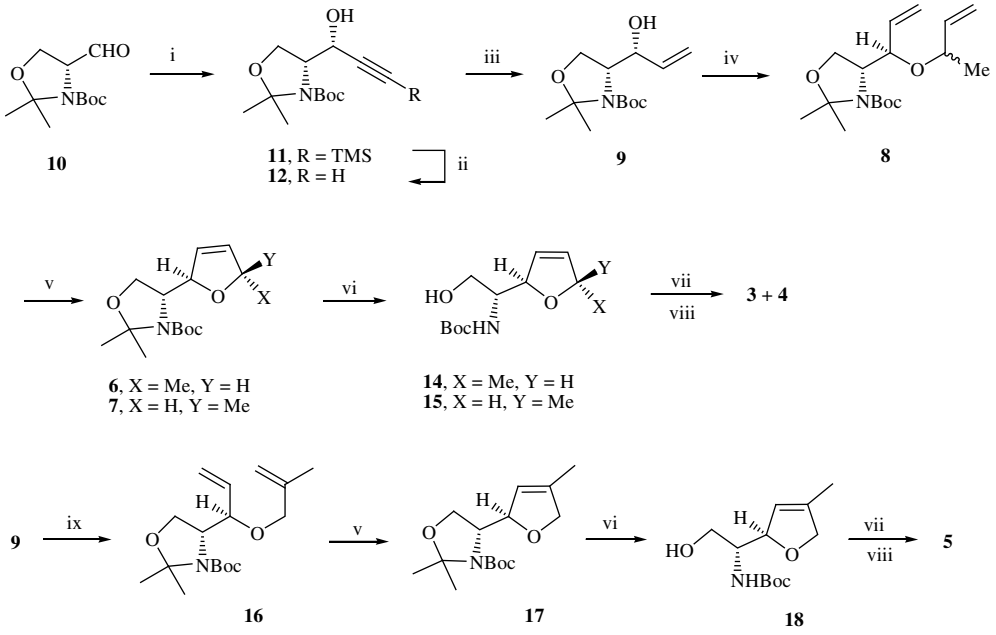


Figure 3.

scaling up. Thus, addition of lithium trimethylsilylacetylide to **10**, prepared following an improved method,[11] proceeded well using the reported procedure for *ent*-**10** to provide a separable mixture of the *syn*-propargyl alcohol **11** together with the corresponding *anti*-isomer (9:1 *syn*:*anti*). Deprotection of the trimethylsilyl group from **11** then led to the acetylene derivative **12** which on partial hydrogenation with Lindlar's catalyst smoothly provided the desired allyl alcohol **9**. Alkylation of the latter with 3-chloro-1-butene using bases such as NaH, KO^{t}Bu or LDA proved to be problematic under a range of conditions, and only low yield and conversion (up to 20%) to the desired **8** was observed in each case. However, the use of silver oxide significantly improved the conversion and a moderate but consistent yield (61%) of **8** was realised. Attempted ring-closing metathesis of the mixture of dienes **8** with Grubbs' first generation catalyst,[12] benzylidene bistricyclohexylphosphinoruthenium(IV) dichloride, proved to be unsuccessful under a range of conditions. Pleasingly, the use of Grubbs' second generation catalyst, benzylidene [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)-ruthenium[13] **13**, effected smooth ring closure and the desired cycloalkenes, **6** and **7**, were obtained in good yield but as an inseparable mixture. Examination of ^{1}H NMR spectrum and HPLC of the mixture of products **6** and **7** quickly revealed that the mixture was slightly enriched (1: 1.2–1.5 in various runs) with one isomer, although the identity of the major isomer was difficult to assess at this stage. Diastereoselectivity in the RCM reaction of diene mixtures has been observed in many instances.[14] However, attempts to increase the diastereoselectivity in the cyclisation of **8** unfortunately did not meet with further success. Preliminary molecular modelling studies indicated that the *trans*- and the *cis*-isomers, **6** and **7**, were of similar energy and reacted with similar rates under the Grubb conditions. Acid-catalysed deprotection of the oxazolidine unit present in the mixture of products **6** and **7** using *p*-toluenesulfonic acid in methanol led to the formation of the mixture of the alcohols **14** and **15** in very good yield. However, the products also proved to be difficult to separate by column chromatography. Accordingly, the mixture of alcohols was subjected to a two-step oxidation to the corresponding carboxylic acids involving initial



Scheme 1. Reagents and conditions: (i) trimethylsilylacetylene, *n*-BuLi, $ZnBr_2$, Et_2O −78 °C to rt, 18 h, 76%; (ii) NH_4F, *n*-$Bu_4N^+HSO_4^-$, CH_2Cl_2, rt, 1 h, 80%; (iii) Lindlar's catalyst, H_2, EtOAc, 0.5 h, 96%; (iv) 3-chloro-1-butene (4 equiv), *n*-$Bu_4N^+Br^-$ (1 equiv), Ag_2O (1.5 equiv), *N*,*N*-DMF, rt, 21 h, 61%; (v) Grubbs' catalyst **13** (7 mol %), PhH, reflux, 36 h, **6** + **7** (66%), 48 h for **17** (56%); (vi) *p*-toluenesulfonic acid (0.1 equiv), MeOH, rt, 1.5 h, **14** + **15** (94%), **18** (93%); (vii) Dess–Martin periodinane (1.3 equiv), CH_2Cl_2, rt, 1 h; (viii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, ^{t}BuOH, H_2O, rt, 12 h, **3** (41%), **4** (33%); **5** (77%); (ix) methallyl bromide (4 equiv), *n*-$Bu_4N^+Br^-$ (1 equiv), Ag_2O (1.5 equiv), *N*,*N*-DMF, rt, 12 h, 79%.

formation of the corresponding aldehydes using Dess–Martin reagent[15] followed by Pinnick oxidation[16] of the latter to compounds **3** and **4** in a combined yield of 74% over two steps. The mixture of products **3** and **4** was then separated by preparative HPLC on a reverse-phase column using gradient elution with a solvent combination of acetonitrile and water-containing trifluoroacetic acid (0.1%). The major isomer was found to be *N*-Boc-furanomycin **3**, $[\alpha]_D$ = +179 (*c* 1.5, $CHCl_3$), which showed spectroscopic properties[17] in close agreement to those reported.[3c,4e] Compounds **3** and **4** exhibited carbamate rotamers in their ^{1}H NMR spectra recorded at room temperature. However, well-resolved spectra were obtained at 50 °C. We also noticed a significant difference in the resonance of the 5′-methyl group in the ^{1}H NMR spectra of the mixture of compounds **6** and **7**, **14** and **15** and **3** and **4**, in which the methyl group of the major isomer consistently appeared upfield (δ 1.20–1.24) compared to that of the minor isomer (δ 1.30–1.35). This was also reflected in the spectra of purified **3** and **4**. Thus, the diastereoselectivity in the RCM reaction of the mixture of the dienes **8** was assigned in favour of the *trans*-isomer **6** (Scheme 1).

Similarly, alkylation of **9** with methallyl bromide under the developed conditions led to the formation of the substituted allyl ether **16**. Ring-closing metathesis of the latter proved to be even more sluggish and proceeded with a modest yield of 56% under forcing conditions to provide **17**. This result is in line with some of the observations[18] made during the formation of tri-substituted olefins by RCM reaction in other instances. Compound **17** was then converted into the isofuranomycin derivative **5** following the three step sequence detailed above. Thus, acid-catalysed deprotection of the oxazolidine unit in **17** led to the formation of the primary alcohol **18**, which was sequentially oxidised to the carboxylic acid derivative **5** in 71% overall yield of over three steps.

3. Conclusion

In short, we have developed a concise synthesis of the *N*-Boc-furanomycin derivative **3** in an overall yield of 9% from Garner's aldehyde **10** in a linear sequence of eight steps. The synthesis constitutes a formal synthesis of furanomycin since conversion of **3** to furanomycin is well documented.[3c,4e] The methodology developed is simple and short, and it avoids the use of less accessible chiral reagents. It also allows syntheses of the 5′-epi-furanomycin derivative **4** and the isofuranomycin derivative **5** from a common intermediate involving nearly identical reaction sequences. Previous syntheses[4a,d,e,5a,b] of furanomycin and/or its isomers from a common intermediate involved somewhat longer sequences and also involved separation of stereoisomers at some stage in common with our procedure. The methodology developed is expected to find application in the preparation of other isomeric furanomycin derivatives relevant to protein engineering. Work will be continued along these directions in this laboratory.

Acknowledgements

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17. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for **3**: Mp: 150–151 °C. $[\alpha]_D$ = +179 (*c* 1.51, $CHCl_3$). IR (KBr): 3445, 1733, 1662, 1528, 1410 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 5.95 (1H, ddd, *J* = 1.6, 2.2, 6.3), 5.78 (1H, ddd, *J* = 1.6, 2.4, 5.4), 5.37–5.34 (1H, m), 5.12 (1H, br d, *J* = 9.1), 5.06–5.02 (1H, m), 4.47–4.44 (1H, m), 1.44 (s, 9H), 1.24 (3H, d, *J* = 6.4). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 174.4, 155.8, 133.6, 125.8, 86.1, 83.6, 80.0, 56.8, 28.2, 21.5. HRMS (TOF MS ES+): obsd 280.1166 (M+Na); calcd 280.1161.
Compound **4**: Mp: 97–99 °C $[\alpha]_D$ = +89 (*c* 1.30, $CHCl_3$). IR (KBr): 3440, 1730, 1672, 1518, 1408, 1371 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 5.89 (1H, dt, *J* = 1.6, 6.4), 5.77 (1H, dt, *J* = 1.6, 6.3), 5.31–5.29 (1H, m), 5.10 (1H, br s), 4.96–4.92 (1H, m), 4.50–4.47 (1H, m), 1.45 (9H, s), 1.33 (3H, d, *J* = 6.4). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 173.8, 155.8, 133.8, 126.4, 86.8, 83.0, 80.1, 56.1, 28.5, 21.9. HRMS (TOF MS ES+): obsd 280.1169 (M+Na); calcd 280.1161.
Compound **5**: $[\alpha]_D$ = +72 (*c* 0.21, $CHCl_3$): IR ($CHCl_3$): 3406, 1701, 1059, 772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 5.40 (1H, s), 5.30 (1H, s), 5.15 (1H, br s), 4.56 (1H, br s), 4.49–4.47 (2H, m), 1.77 (3H, s), 1.43 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C): δ 174.5, 155.8, 138.6, 119.9, 87.3, 80.0, 78.9, 56.8, 28.2, 12.2. HRMS (TOF MS ES+): obsd 280.1165 (M+Na); calcd 280.1161.
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