Synthesis of a Biologically Active Analogue of Antibiotic A-32390A

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The total synthesis of a biologically active analogue of antibiotic A-32390A is described.

For some years we have been interested in the synthesis and biosynthesis of fungal metabolites containing the isonitrile functionality.[1] Central to our syntheses of isonitrins A and B was the development of new methodology for the preparation of vinyl formamides from thiooximes.[1–3] Subsequent dehydration with trifluoromethane sulfonic anhydride afforded the corresponding vinyl isonitrile.[4] In an effort to further define the scope and limitations of these reactions we have examined systems pertinent to A-32390A **1**, an antibiotic isolated from a fungus of the genus *Pyranochaeta*[5] (Fig. 1). Schöllkopf *et al.* have synthesised **1** along with a number of structural variants of both the 'carbohydrate portion' and the vinyl isonitrile fragment and demonstrated their efficacy against various bacterial and fungal strains.[6,7]

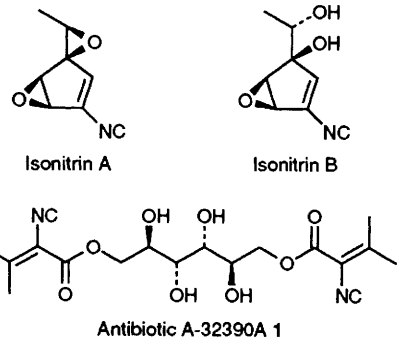
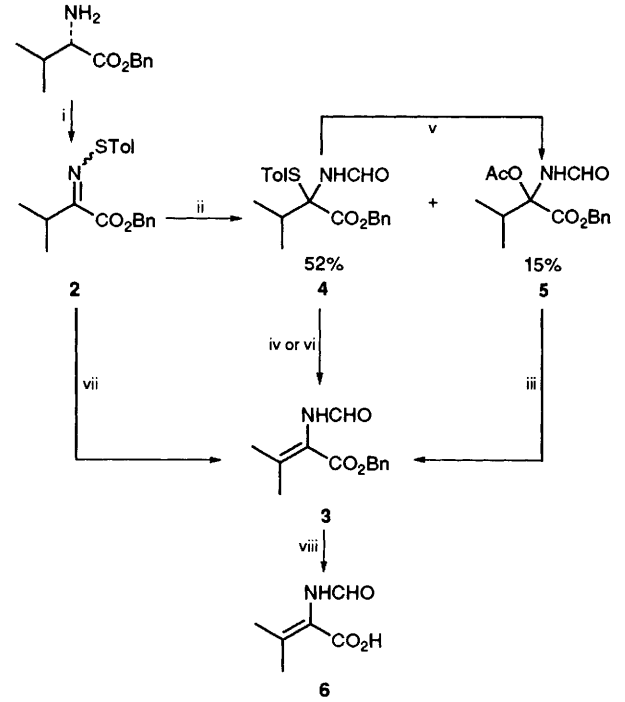


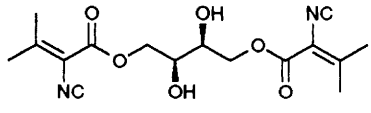
Fig. 1

As no precedent existed for the rearrangement of α-carboxy thiooximes to vinyl formamides studies were first undertaken on simple systems. To this end thiooxime **2** was prepared from L-valine benzyl ester according to the method of Gordon.[8] Exposure of **2** to the rearrangement conditions failed to deliver any of the desired vinyl formamide **3**, however, two *N*-formylated products, the α-thioformamide **4** and the α-acetoxyformamide **5** were isolated in reasonable yield.† Preliminary experiments indicated that while the minor, α-acetoxy formamide **5**, underwent facile elimination to the desired vinyl formamide upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), treatment of the α-thioformamide **4** under equivalent conditions gave rise to a sluggish reaction and only a modest (40%) yield of **3**. Treatment of **4** with $Hg(OAc)_2$–Et_3N was found to lead smoothly to **5** in 86% yield. However, a combination of $Hg(OAc)_2$ and DBU in the same pot gave a 70% yield of the vinyl formamide **3** directly. Thus the desired transformation of **2** to **3** could be achieved by sequential treatment of the thiooxime **2** with PPh_3, $Hg(OAc)_2$ and DBU to afford the vinyl formamide **3** in 55% overall yield. Hydrolysis of **3** afforded the free acid **6**, a key intermediate in Schöllkopf's synthesis of A-32390A **1**,[6] (Scheme 1). Dehydration of **3** proceeded uneventfully to deliver the isonitrile in good yield under previously described conditions.[4,9]

We sought to apply the modified methodology to a total synthesis of **7**, a biologically active analogue of A-32390A **1**.[6] Thus **7** can be disconnected to the erythritol fragment and two identical vinyl isonitrile portions. The stereochemistry of the central portion suggested that it could be prepared from a suitable L-tartrate ester while the vinyl isonitriles would be prepared as described above. Thus diethyl L-tartrate was protected as its *tert*-butyldimethylsilyl (TBDMS) ether[10] and reduced with $LiEt_3BH$[11] to afford **10**. At this point we elected to attach the amino acid residues to the central portion prior to establishing the vinyl formamide in order to probe the thiooxime to the vinyl formamide rearrangement in a more demanding environment. The resulting primary diol **10** was coupled to L-*N*-*Z*-valine using 1,3-dicyclohexylcarbodiimide (DCC)–4-dimethylaminopyridine (DMAP)[12] then deprotected by hydrogenolysis to afford the free diamine **11** in essentially quantitative yield over the two steps. Treatment of **11** with 6 equiv. of *p*-TolSCl in the presence of propylene oxide[8] smoothly converted **11** to the thiooxime **12** as a mixture of geometric isomers. After treatment of **12** with acetic formic anhydride–PPh_3 then $Hg(OAc)_2$ the ^1H NMR spectrum of crude product indicated that the desired α-acetoxy compound had indeed formed but silica gel chromatography led to complete decomposition, thus we effected an *in situ* elimination to deliver vinyl formamide **13**. Unfortunately this very polar compound co-eluted with the triphenylphospine oxide. This practical problem was resolved by use of polymer



Scheme 1 *Reagents and conditions*: i, *p*TolSCl (3 equiv.), propylene oxide (50 equiv.), 4 Å mol. sieves, CH_2Cl_2, 2 h, room temp., 91%; ii, PPh_3 (3 equiv.), acetic formic anhydride (3 equiv.), propylene oxide (10 equiv.), CH_2Cl_2, room temp; iii, DBU (5 equiv.), CH_2Cl_2, 30 min, room temp., 70%; iv, DBU (5 equiv.), CH_2Cl_2, 48 h, room temp., 40%; v, $Hg(OAc)_2$, (1 equiv.), Et_3N (5 equiv.), CH_2Cl_2, 10 min, room temp., 80%; vi, $Hg(OAc)_2$ (1 equiv.), DBU (5 equiv.), CH_2Cl_2, 15 min, room temp., 70%; vii, PPh_3 (3 equiv.), acetic formic anhydride (3 equiv.), propylene oxide (10 equiv.), CH_2Cl_2, 24 h, room temp. then $Hg(OAc)_2$ (3 equiv.) then DBU (5.5 equiv.), 55%; viii, LiOH (1.1 equiv.), THF–H_2O 4 : 1 then H_3O^+, 85%



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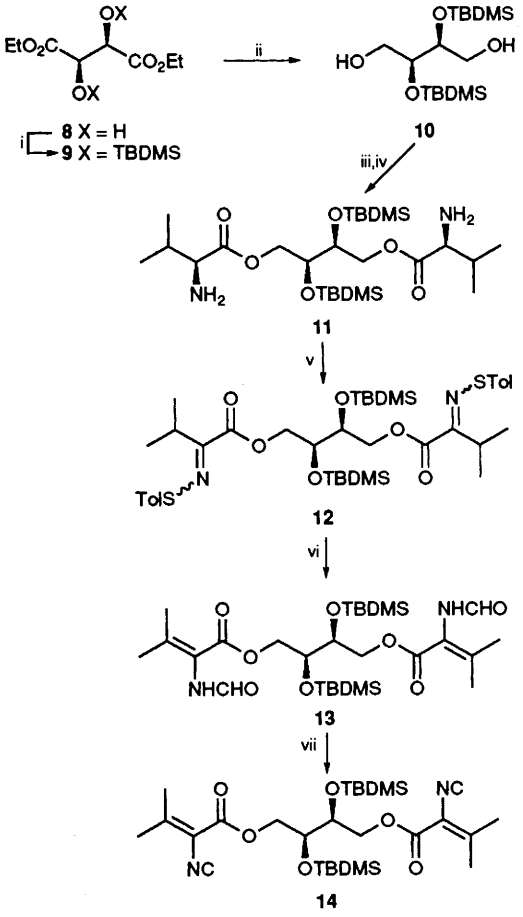
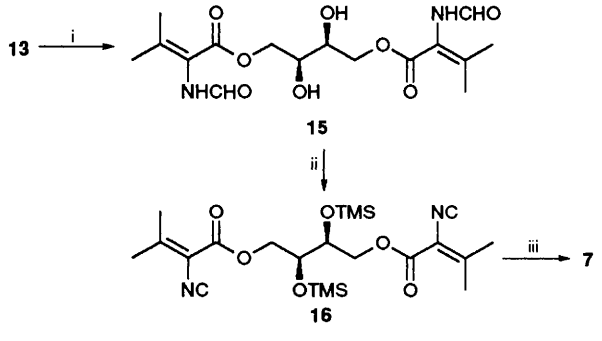


Scheme 2 *Reagents and conditions*: i, TBDMSCl (2.4 equiv.), imidazole (5 equiv.), dimethylformamide (DMF), 14 h, 35 °C, quant.; ii, $LiEt_3BH$ (6 equiv.), THF, 30 min, 0 °C, 75%; iii, L-*N*-*Z*-valine (2.1 equiv.), DCC (2.1 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 24 h, room temp., quant.; iv, H_2, 10% Pd/C, EtOAc, quant.; v, *p*-TolSCl (6 equiv.), propylene oxide (100 equiv.), 4 Å mol. sieves, CH_2Cl_2, 3 h, room temp., 85%; vi, polymer supported PPh_3 (6 equiv.), acetic formic anhydride (6 equiv.), propylene oxide (20 equiv.), CH_2Cl_2, 24 h, room temp., then $Hg(OAc)_2$ (2 equiv.) then DBU (5 equiv.), room temp., 68%; vii, Tf_2O (2 equiv.), Pr^i_2EtN (12 equiv.), CH_2Cl_2, 30 min, −78 °C, 82%



Scheme 3 *Reagents and conditions*: i, 90% formic acid, 4 h, room temp., quant.; ii, TMSCN, DMF then Tf_2O (2 equiv.), Pr^i_2EtN (12 equiv.), CH_2Cl_2, 30 min, −78 °C, 79%; iii, methanolic citric acid, 15 min, room temp., 85%

supported triphenylphosphine[13,14] which could be removed by filtration to afford **13** as a crystalline solid, (Scheme 2).

Vinyl formamide **13** was dehydrated to the isonitrile **14** in 82% yield upon treatment with 2 equiv. of Tf_2O in the presence of Pr^i_2EtN (12 equiv.).[4,9] Attempted deprotection with a variety of fluoride sources led to complete decomposition presumably *via* hydrolysis of the ester linkages by residual water in the fluoride source. Thus we were forced to exchange protecting groups at the vinyl formamide stage. The TBDMS groups were quantitatively removed by stirring with 90% formic acid at room temp. for 4 h. The resulting crystalline diol-formamide **15** has been prepared previously by Schöllkopf[6] and as such represents a formal total synthesis. In order to effect dehydration to an isonitrile Schöllkopf employed prior protection of the hydroxy groups as formate esters. However, they experienced significant decomposition of the target molecule during the final base catalysed deprotection.[6] In an effort to overcome this problem the diol was blocked with trimethylsilyl (TMS) groups[15] and the crude product was dehydrated to afford **16** in 79% yield over two steps. The TMS groups were successfully removed in 85% yield by a brief exposure to methanolic citric acid,[16] to afford **7**,‡ (Scheme 3).

In summary, the methodology for the preparation of vinyl isonitriles from thiooximes has been extended to α-carboxy systems and applied to the total synthesis of a biologically active analogue of the natural product, Antibiotic A-32390A **1**.

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Footnotes

† A discussion of the mechanism will appear in a forthcoming full paper.

‡ Compound **7** had identical chemical and physical data to that reported previously.

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