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Synthesis of racemic brevioxime

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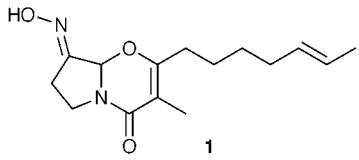
Amine hydrochloride 12 and β-keto thioester 16 were coupled and treated with TFA; the resulting alcohols 18 were oxidized and converted into a mixture of oximes 20, from which the major product, racemic brevioxime 1, was isolated.

We report the synthesis of brevioxime **1** in racemic form. Natural brevioxime, which is optically active, was isolated[1] from the fungus *Penicillium brevicompactum* Dierckx, and is of



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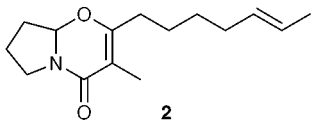

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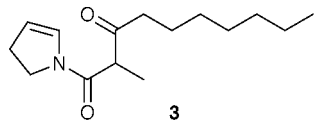

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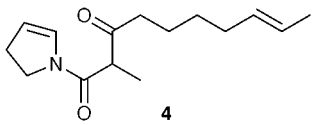

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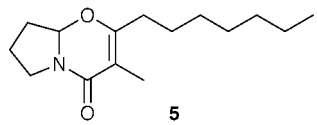

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potential value as a lead compound in pesticide research because it is an inhibitor of juvenile hormone biosynthesis.[1] The related compounds **2**,[2] **3**[3] and **4**[2] have been obtained from the same fungus. The last two are also inhibitors of juvenile hormone and, while **2** shows insecticidal activity, its primary mode of action does not appear to have been established.

The structure of brevioxime is of an unusual type, and the natural products **1** and **2**, together with the totally synthetic **5**,[3] appear to be the only representatives.†

Our synthetic plan, which was developed after a number of exploratory experiments,‡ was based on the idea that an amide aldehyde of type **6** (Scheme 1) should cyclize[5,7] in the presence of acid, so as to generate the required heterocyclic system directly (**6** → **7** → **8**).

On the basis of the above considerations, we first made the amine hydrochloride **12**. Preparation of this compound was initially troublesome, but we eventually found that it is accessible by the route summarized in Scheme 2. Epoxy acetal **9**, readily available by epoxidation (HOCl, water, < 5 °C; 72%) of acrolein dimethyl acetal,[8] was treated with potassium cyanide (KCN, EtOH–water, room temperature, 24 h; 62%),[9] so as to afford the cyano alcohol **10**, which was protected by silylation (Bu^tMe_2SiCl, Et_3N, CH_2Cl_2, reflux, overnight; 81%). The nitrile function of **10** was then reduced by catalytic hydrogenation in the presence of 6 equiv. of $CHCl_3$ (PtO_2, dry EtOH, $CHCl_3$, 50 psi, 24 h, room temperature; 64–75%);[10] other conditions§ were unsuccessful.

With the amine hydrochloride in hand, the next task was to convert it into a β-keto amide (*cf.* **6**). The preparation of such amides is often best done by treating a β-keto thioester with an amine;[11] in the present case the appropriate β-keto thioester was **16**. We initially made this compound by alkylation of the simple thioester **13**[12] with (*E*)-6-iodohex-2-ene, using the technique of double deprotonation,[13] but the yield was poor (33%). A better route involved acylation[14] of thioester **15**[15] with the imidazolide derived from the known (*E*)oct-6-enoic acid.[16] Under optimum conditions,¶ the required β-keto thioester **16** can be obtained in 64% from acid **14** (Scheme 3).

The amino component and the thioester were coupled by condensation in the presence of silver triflate[11]‖ [**12** + **16** → **17**; Et_3N (2 equiv.), AgOTf (2 equiv.), THF, room temperature, 30 min; 92%]. At this point, exposure to aqueous TFA [50% aq. TFA, $CHCl_3$ (1:2)] brought about the intended series of cyclizations (see Scheme 1), and gave an almost quantitative yield of the desired alcohols **18**, as a 1:1 mixture of diastereoisomers. The chromatographically less polar isomer was easily oxidized by the Dess–Martin reagent (CH_2Cl_2, 2 h, *ca.* 100%), taking the route as far as ketone **19**. The isomeric alcohol was more difficult to oxidize, but it did react with tetrapropylammonium perruthenate (TPAP)[18] [TPAP, NMO, CH_2Cl_2, 4 Å molecular sieves, 2 h; 23%, after correction for recovered starting material (19%)]. Treatment of ketone **19** with hydroxylamine hydrochloride under classical conditions[19] [hydroxylamine hydrochloride (5 equiv.), NaOAc (5.2 equiv.), water, EtOH, 2 h; *ca.* 100%] gave the oximes **20**, with the desired *E*-isomer predominating (4.3:1). This isomer was readily separated by chromatography, so as to afford racemic brevioxime, whose spectroscopic properties (^1H NMR, ^{13}C NMR) were the same as those reported for material isolated from the natural source.

The above route illustrates the utility of the cyclization of an amide nitrogen onto an aldehyde carbonyl for generating certain nitrogen heterocycles. The route is short, if one ignores the simple steps needed to prepare acid **14**, and the approach is convergent, and it should be amenable to the synthesis of analogues.

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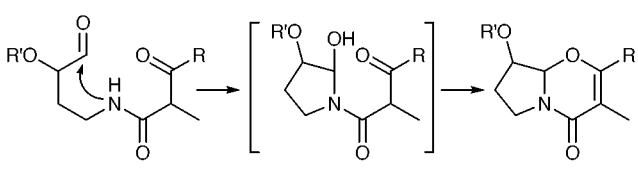
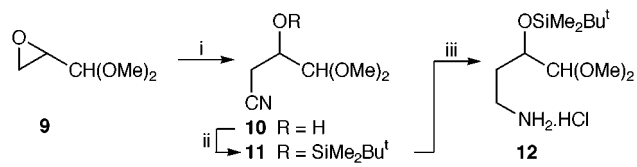


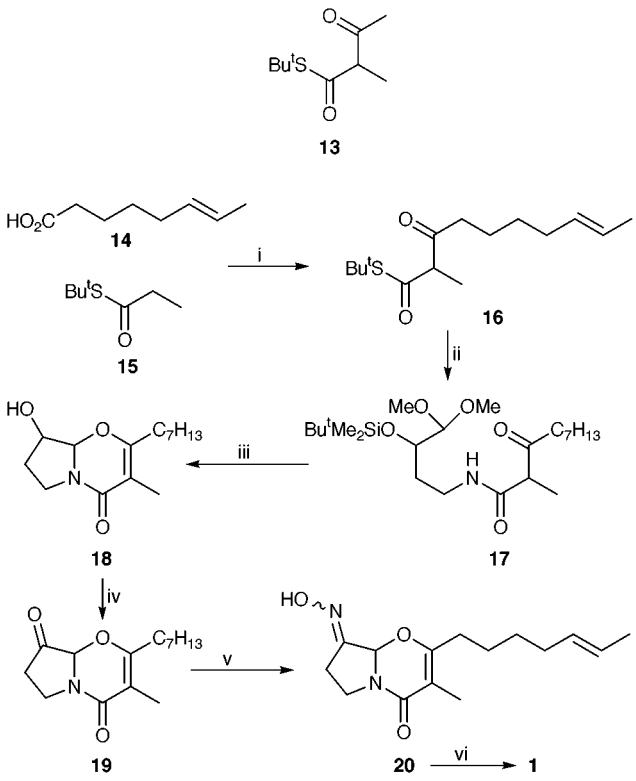
6 **7** **8**

Scheme 1



9 **10** R = H; **11** R = $SiMe_2Bu^t$; **12**

Scheme 2 *Reagents and conditions*: i, KCN, EtOH–water, room temp., 24 h, 62%; ii, Bu^tMe_2SiCl, Et_3N, CH_2Cl_2, reflux, overnight, 81%; iii, PtO_2, dry EtOH, $CHCl_3$ (6 equiv.), 50 psi, 24 h, room temp., 64–75%.



Scheme 3 *Reagents and conditions*: i, see note ¶; ii, amine hydrochloride **12**, Et_3N (2 equiv.), AgOTf (2 equiv.), THF, room temp., 30 min, 92%; iii, 50% aq. TFA, $CHCl_3$ (1 : 2), *ca.* 100%; iv, Dess–Martin reagent, CH_2Cl_2, 2 h, *ca.* 100%; for more polar alcohol, TPAP, NMO, CH_2Cl_2, 4 Å molecular sieves, 2 h, 23%, after correction for recovered alcohol (19%); v, hydroxylamine hydrochloride (5 equiv.), NaOAc (5.2 equiv.), water, EtOH, 2 h, *ca.* 100%; vi, flash chromatography over silica gel.

Notes and references

† However, benzo-fused analogues, such as 1,2,3,3a-tetrahydro-9*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-9-one, are known (see *e.g.* ref. 4), as are substances lacking the 2,3-double bond (see *e.g.* ref. 5).

‡ These were based on *N*-acyl-2-pyrrolines (*cf.* ref. 6).

§ We also tried reduction with $LiAlH_4$ or Pd-C/H_2.

¶ The acid was first converted into its imidazolide (1,1′-carbonyldiimidazole, THF, 0 °C to room temperature, 30 min). The thioester **15** was deprotonated (LDA, THF, −78 °C, 10 min), and the resulting enolate (3 equiv.) was added by cannula to the imidazolide (−78 °C). After 30 min, the cold bath was removed and, after a further 5 min, the mixture was quenched with saturated aqueous ammonium chloride. Instead of the imidazolide, the corresponding derivative of 2,2′-carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) can be used (*cf.* ref. 17), in which case only 1 equiv. of **15** is required.

‖ We used AgOTf instead of $AgOCOCF_3$ (ref. 11). The AgOTf was added in one portion to a stirred solution of the other components.

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