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Studies directed towards the total synthesis of feigrisolide B☆

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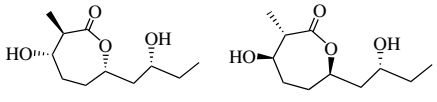
Abstract—Attempts directed towards the total synthesis of feigrisolide B resulted in the synthesis of lactones **1** and **2**. The synthesis of **1** and **2** was achieved from D-glucose and L-malic acid, respectively, with a Ti(IV) mediated diastereoselective aldol reaction as the key step. The structures of both **1** and **2** revealed that the structure proposed for feigrisolide B is incorrect.

1. Introduction

Thiericke et al.[1] have isolated four new lactone compounds named feigrisolides A to D from *Streptomyces griseus*. Structurally, feigrisolides A and B are hepta-lactones, while feigrisolides C and D are 16 membered macrolides. Feigrisolide B exhibits strong antibacterial, as well as medium cytotoxic and antiviral activities. Feigrisolides A, C and D are medium inhibitors of 3α-hydroxy steroid dehydrogenase (3α-HSD) inhibiting activity. Thiericke et al. confirmed the relative stereochemistry of the ring of feigrisolide B based on NOESY NMR experiments and established the absolute configuration at C-8 as R by Helmchen's method[2] and proposed **1** as the structure of feigrisolide B. A major goal of the present first total synthesis for feigrisolide B was to establish the absolute configuration of the natural compound. Herein, we report our attempts directed towards the total synthesis of feigrisolide B, which resulted in the synthesis of lactones **1** and **2**.



1

2

2. Results and discussion

Antithetic analysis revealed that **1** could be synthesised from *seco* acid **3**. A diastereoselective aldol reaction on aldehyde **4** was envisaged to give the alcohol with a complete array of stereocentres, which would give **3**, while **4** would be derived from D-glucose, wherein the C-2 and C-4 hydroxy centres of D-glucose are retained as C-6 and C-8 stereocentres in the target molecule, respectively. Thus, a C-6 framework along with two stereocentres are derived from D-glucose, while the remaining two stereocentres are introduced by 'non-Evans' aldol condensation (Scheme 1).

Accordingly, the known[3] olefin **7**, prepared from D-glucose, on methanolysis with catalytic H_2SO_4 in methanol (Scheme 2), gave methyl glycosides **8**. Alkylation of **8** with NaH/BnBr in THF afforded **9** (75%), which on treatment with 60% aq AcOH and catalytic H_2SO_4, afforded lactols **10**. $NaBH_4$ reduction of lactols **10** in methanol gave diol **11** (90%). Reaction of **11** with trityl chloride and Et_3N gave trityl ether **12** (78%), which on further reaction with TBDPSCl and imidazole, furnished **13** (70%). Further, deprotection of the trityl group in **13** with trifluoroacetic acid in CH_2Cl_2 afforded alcohol **14**.

IBX oxidation of **14** in DMSO gave **15**, which on subsequent reaction with (carbethoxymethylene)triphenylphosphorane afforded **16** (79%). Catalytic hydrogenation of **16** with PtO_2 and further reduction of **17** with LAH in THF gave **18** (88%). Alcohol **18** was oxidised with IBX to afford **4** (90%). The addition

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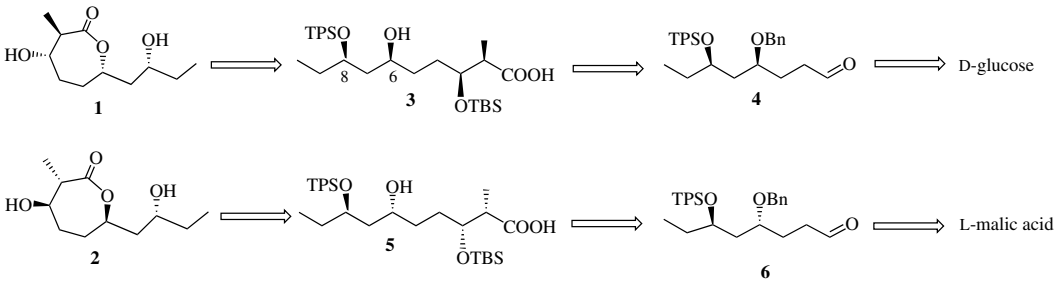
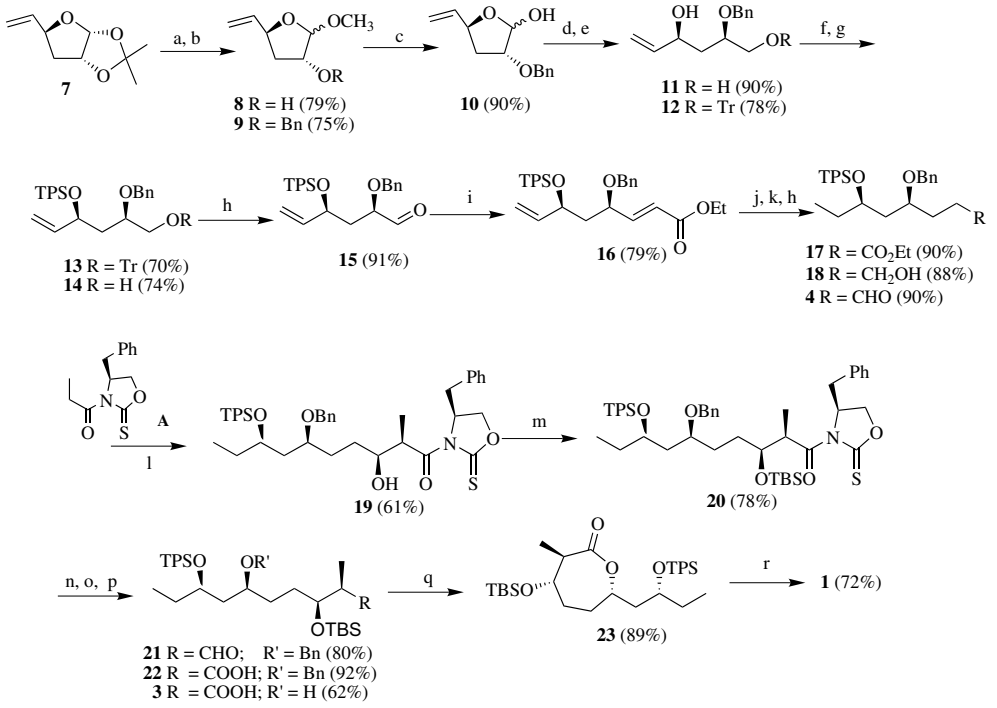


Scheme 1. Retro synthesis of **1** and **2**.



Scheme 2. Reagents and conditions: (a) cat. H_2SO_4, MeOH, 60 °C, 12 h; (b) NaH, BnBr, THF, rt, 6 h; (c) cat. H_2SO_4, 60% aq AcOH, 60 °C, 12 h; (d) $NaBH_4$, MeOH, rt, 1 h; (e) TrCl, Et_3N, CH_2Cl_2, rt, 4 h; (f) TBDPSCl, imidazole, CH_2Cl_2, rt, 4 h; (g) trifluoroacetic acid, CH_2Cl_2, 0 °C, 1 h; (h) IBX, DMSO, rt, 6 h; (i) PPh_3=CHCOOEt, benzene, 80 °C, 1 h; (j) PtO_2, EtOAc, H_2, rt, 12 h; (k) LAH, THF, rt, 1 h; (l) **A**, $TiCl_4$, DIPEA, CH_2Cl_2, 0 °C, 30 min then **4** at −78 °C, 30 min; (m) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 30 min; (n) DIBAL-H, CH_2Cl_2, −78 °C, 15 min; (o) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, rt, 3 h; (p) DDQ, aq CH_2Cl_2 (19:1), 40 °C, 5 h; (q) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, 90 °C, 14 h; (r) HF–pyridine, pyridine, THF, 2 days.

of the titanium enolate derived from propanoyl oxazolidinethione **A** to **4**, gave the 'non-Evan's *syn* aldol[4] product **19** as the only isolable diastereomer in 61% yield. Adduct **19** was treated with TBDMSOTf and 2,6-lutidine in CH_2Cl_2 to afford **20**, which on further treatment with DIBAL-H in CH_2Cl_2 at −78 °C gave **21** (80%). Oxidation of **21** with $NaClO_2$ and NaH_2PO_4 in *t*-BuOH gave acid **22** (92%), which on debenzylation with DDQ afforded the *seco* acid **3**. Lactonisation of **3** under Yamaguchi reaction conditions[5] and deprotection of the two silyl ethers by treatment with HF–pyridine complex afforded **1** in 72% yield. The structure of **23** was unambiguously assigned based on the spectral and NOE studies (Fig. 1).

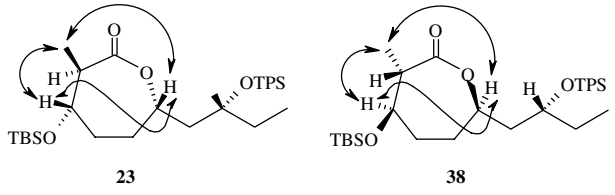


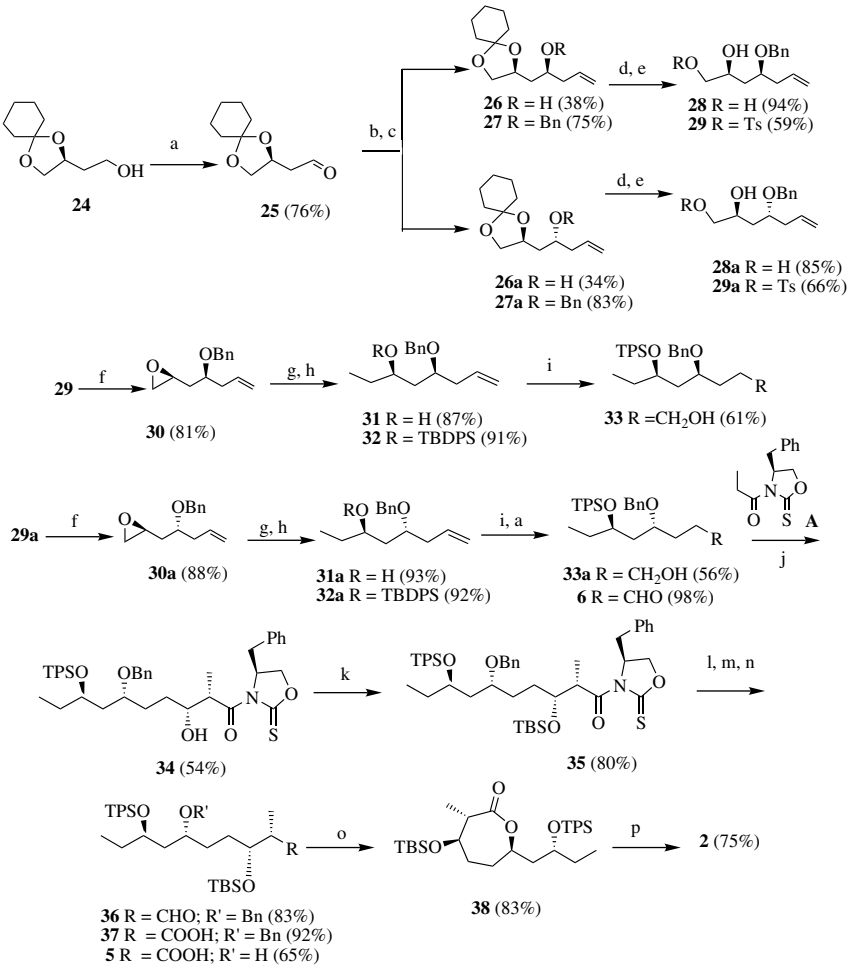
Figure 1. NOE studies on **23** and **38**.

The spectroscopic data (Table 1) and specific rotation value $[\alpha]_D = -39.1$ (*c* 0.23, $CHCl_3$) of **1** did not correspond to the spectroscopic data and specific rotation[1] of feigrisolide B with $[\alpha]_D = 0$ (*c* 0.2, CH_3OH). This synthesis thus implies that the proposed structure[1] for feigrisolide B is incorrect. Hence, to arrive at the first synthesis of feigrisolide B and to determine the absolute stereochemistry as well, a further study was undertaken for the synthesis of **2**, with enantiomeric C-2, -3 and -6 stereocentres, as indicated in retro analysis (Scheme 1), starting from L-malic acid.

Table 1. ^{1}H NMR (500 MHz, $CDC1_3$) and ^{13}C (75 MHz, $CDC1_3$) data of the feigrisolide B and **1**, **2**

Position	Feigrisolide B[1]		**1**		**2**	
	δ ^{13}C	δ H^1 (multi, J=Hz)	δ ^{13}C	δ H^1 (multi, J=Hz)	δ ^{13}C	δ H^1 (multi, J=Hz)
1	177.6		176.6		178.4	
2	45.3	2.50 (dq, 8.3, 7.0)	46.3	3.22 (dq, 7.55, 5.22)	51.7	3.15 (dq, 8.05, 6.59)
3	81.0	3.98 (br q, 8.3)	77.9	3.905 (m)	76.9	3.84 (m)
4	29.1	2.03 (α, m)	29.8	2.08 (α, m)	30.4	2.10 (α, m)
		1.68 (β, m)		1.86 (β, m)		1.79 (β, m)
5	30.6	1.65 (α, m)	31.8	1.70 (α, m)	31.3	1.66 (α, m)
		2.01 (β, m)		1.98 (β, m)		1.95 (β, m)
6	77.3	4.21 (m)	72.2	4.65 (m)	71.22	4.73 (m)
7	40.7	1.70 (m)	44.4	1.98 (m)	44.6	1.95 (m)
8	70.4	3.78 (m)	70.9	3.72 (m)	70.3	3.84 (m)
9	29.9	1.51 (m)	31.0	1.52 (m)	31.0	1.46 (m)
10	10.0	0.92 (t, 7.5)	11.1	0.96 (t, 7.5)	11.1	0.98 (t, 7.5)
1′	13.7	1.16 (d, 7.0)	14.5	1.38 (d, 7.8)	14.7	1. 39 (d, 7.55)

Accordingly **24**[6], derived from L-malic acid, was treated with IBX in DMSO to give **25** (Scheme 3), which on further treatment with allyl bromide and activated zinc in THF–aq NH_4Cl at 0 °C, under Barbier reaction conditions,[7] gave carbinols **26** (38%) and **26a** (34%) as a separable diastereomeric mixture (60/120 silica gel, 1:16



Scheme 3. Reagents and conditions: (a) IBX, DMSO, rt, 6 h; (b) allyl bromide, activated zinc, THF–aq NH_4C1 solution, 0 °C–rt, 4 h; (c) BnBr, NaH, THF, rt, 6 h; (d) CSA, MeOH–H_2O, rt, 12 h; (e) TsCl, Et_3N, CH_2C1_2, rt, 16 h; (f) K_2CO_3, MeOH, rt, 1 h; (g) Me_3Al, *n*-BuLi, toluene, −20 °C to rt, 12 h; (h) TBDPSC1, imidazole, CH_2C1_2, rt, 4 h; (i) BH_3–DMS, THF, MeOH, aq NaOH, H_2O_2, rt, 12 h; (j) **A**, $TiCl_4$, TMEDA, CH_2C1_2, 0 °C, 30 min then **6** at −78 °C, 30 min; (k) TBDMSOTf, **2**, 6-lutidine, CH_2C1_2, rt, 30 min; (l) DIBAL-H, CH_2C1_2, −78 °C, 15 min; (m) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, rt, 3 h; (n) DDQ, CH_2C1_2, 40 °C, 5 h; (o) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, 90 °C, 14 h; (p) HF–pyridine, pyridine, THF, 2 days.

EtOAc–hexane). A few more steps were carried out on both diastereomers. Thus, **26** and **26a** were converted into benzyl ethers **27** and **27a**, respectively, and subjected to acid (CSA) catalysed hydrolysis in aq MeOH to give diols **28** and **28a**. Selective tosylation (*p*-TsCl, Et_3N, CH_2Cl_2) of **28** and **28a** and further treatment of **29** and **29a** with K_2CO_3 in CH_3OH afforded the corresponding epoxides **30** (81%) and **30a** (88%). Selective opening of **30** and **30a** with Me_3Al in toluene gave **31** (87%) and **31a** (93%), which on reaction with TBDPSCl–imidazole, furnished **32** and **32a**, respectively. Hydroboration of **32** and **32a** gave **33** (61%) and **33a** (56%). Diastereoisomer **33** was found to be identical in the ^1H NMR and specific rotation data with **18** derived from D-glucose, hence isomer **33a** was used for the further synthesis of **2**.

Accordingly, oxidation of **33a** gave aldehyde **6**, which on aldol reaction with titanium enolate (derived from the treatment of propanoyl oxazolidinethione **A** with $TiCl_4$, TMEDA, CH_2Cl_2), afforded the *syn* aldol[4] adduct **34** (54%), whose structure was unambiguously assigned from NOE studies. Treatment of **34** with TBDMSOTf, controlled reduction of **35** with DIBAL-H and further oxidation of **36** with $NaClO_2$ and NaH_2PO_4 in *t*-BuOH gave acid **37**. Debenzylation of **37** with DDQ gave the *seco* acid **5** (65%), which finally on lactonisation under Yamaguchi conditions gave **38** (Fig. 1), which on desilylation with HF–pyridine complex, afforded **2** (75%). The structure of **38** was thoroughly characterised from NMR studies. The spectroscopic data (Table 1) and specific rotation $[\alpha]_D = -70.0$ (*c* 0.25, $CHCl_3$) of **2** also was found to be different from that of feigrisolide B, reported[1] in the literature.

3. Conclusion

We therefore, can conclude that the structure proposed for feigrisolide B is incorrect. It does not correspond to the proposed structure **1** or its C-2, -3 and -6 epimer **2**. However, synthesis of other enantiomers as well as diastereomers by using diastereoselective aldol reactions may offer an opportunity to arrive at the correct structure of natural product. A comparative study of the spectral and specific rotation values of the derivatives of both the natural and synthetic materials, paves the way for the determination of the structure and absolute stereochemistry of feigrisolide.

Acknowledgements

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