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Total synthesis of 15-deoxoclerocidin

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Abstract

Enantiomerically pure 15-deoxoclerocidin (**14**), 15-dihydro-12-*O*-formylclerocidin (**19**) and 12-*O*-formyl-15,20-tetrahydroclerocidin (**18**) were synthesized from a methyl-substituted Wieland Miescher ketone (**3**).

Keywords: clerocidin; 15-deoxoclerocidin; 15-dihydro-12-*O*-formylclerocidin; 12-*O*-formyl-15,20-tetrahydroclerocidin; synthesis.

Clerocidin (**1**)[1] is a clerodane diterpene which was isolated from *Oidiodendron truncatum* in the form of its methanol adduct (**2**). Shown here in its open chain γ-hydroxyaldehyde form, clerocidin exists in solution as an equilibrium of the corresponding ketolactols and their 1,4-dioxane dimers (Fig. 1).

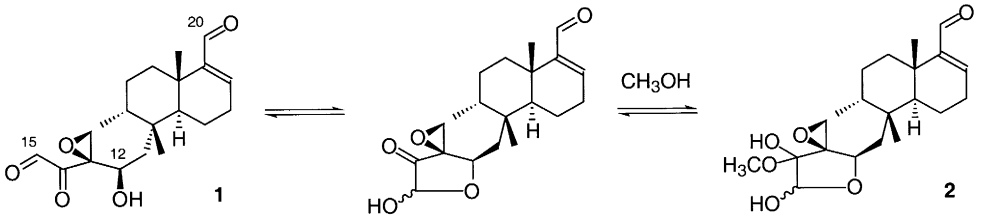

Fig. 1.

Clerocidin is reported to have antibacterial activity and stimulates irreversible topoisomerase II-mediated DNA cleavage.[2] A recent total synthesis of clerocidin[3a] leads us to report here our total synthesis of enantiomerically pure 15-deoxoclerocidin, di- and tetrahydroclerocidin and of **15**, an unexpected rearrangement product obtained by Jacquet upon reacting clerocidin with diazomethane.[4] Our results also provide independent synthetic proof of the absolute configuration of these compounds.

Our synthesis proceeds from the known enantiopure monoketal **3**[5] by Birch reductive alkylation to give the ester **4** in 80% yield (Scheme 1). Wittig methylenation of the ketone gave a 75% yield of the

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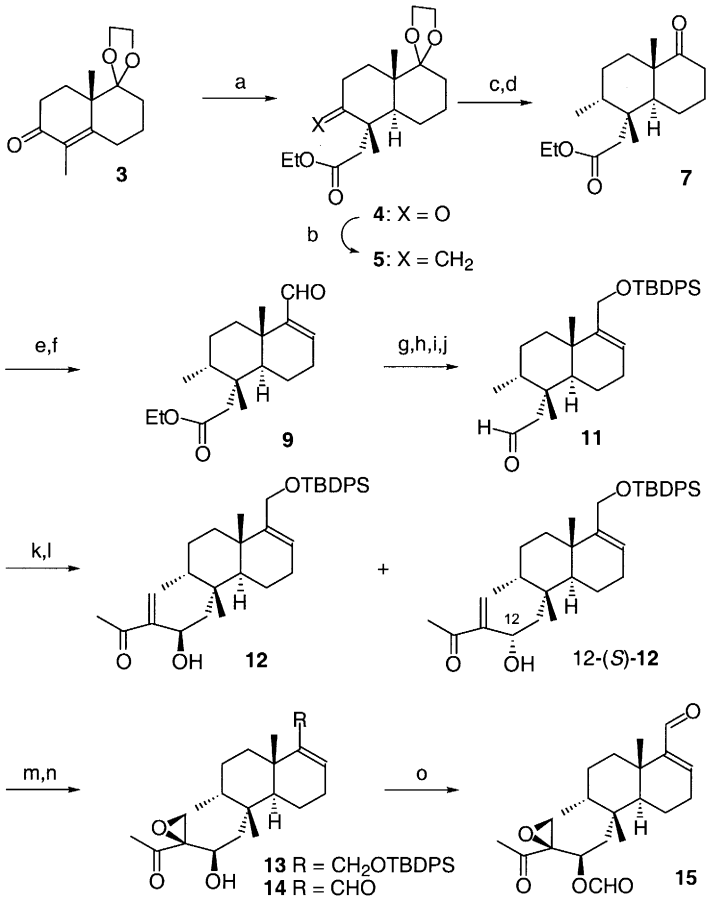
exo-methylene compound **5**,[6] which on hydrogenation over Rh–C gave the desired α-epimer **6** in 80% yield. The configuration at the new established stereocenter was firmly established by comparison of NMR data with literature values of similar compounds.[3b,3c,7]



Scheme 1. Reagents and conditions: (a) Li, NH_3; 1 equiv. H_2O; ICH_2COOEt, 80%; (b) Ph_3PCH_3Br, KO*t*Bu, 75%; (c) H_2, Rh/C, 80%; (d) 1 M aq. HCl, THF, 100%; (e) LDA, $PhN(SO_2CF_3)_2$, 84%; (f) $Pd(OAc)_2$, CO, Bu_3SnH, 84%; (g) $NaBH_4$, $CeCl_3$, MeOH; (h) TBDPSiCl, imidazole, 96%; (i) LAH, ether, 0°C; (j) PCC, CH_2Cl_2, 79%; (k) methyl vinyl ketone, PhSeTMS, TMSOTf; (l) $NaIO_4$, 20% (12-*R*)+45% (12-*S*); (m) *t*BuOOH, $Ti(OiPr)_4$, 4 Å MS, 83%; (n) SeO_2, aq. dioxane, reflux, 5 h, 43%; (o) AcOCHO, pyr., 44%

Ketal hydrolysis of **6** gave ketone **7** in quantitative yield. Numerous attempts to convert **7** to the aldehyde **9** through initial nucleophilic addition of a C1-unit to the ketone carbonyl failed due to enolization. However, reductive carbonylation of the corresponding enol triflate **8** using modified Stille conditions[8] gave the unsaturated aldehyde **9**[9] in 84% yield. The aldehyde was subjected to Luche reduction and protected as the TBDPS ether **10**. The ester side chain was then converted to the aldehyde **11**[10] by a reduction–reoxidation sequence in 79% yield over two steps.

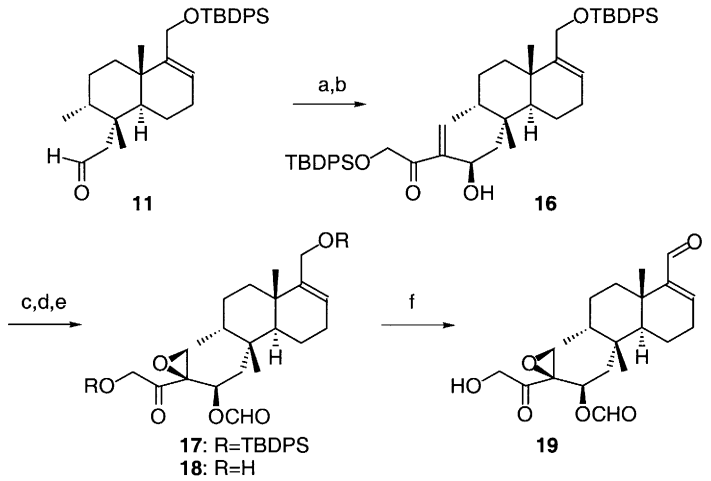
Treatment of **11** with methyl vinyl ketone, PhSeTMS and TMSOTf (1.5:1.5: 0.2 equiv.) gave on $NaIO_4$ oxidation[11] a 1:2.5 ratio of **12**[12] and its 12-*S* diastereoisomer which were easily separated by flash chromatography. Both diastereoisomers of **12** were separately carried forward to **15** and 12-*epi*-**15** to establish the configuration at this stereocenter.

Attempts to use the (*S*,*S*)-enantiomer of Barrett's chiral Lewis acid[13] derived from (−)-tartaric acid,

which has been described for closely related examples of Baylis–Hillman-like reactions, led to much lower yields of a mixture favoring the same (wrong) diastereoisomer. Obviously, stereocontrol by the substrate in this case cannot be overcome by the chiral catalyst.

Epoxidation of allylic alcohol **12** with *t*-BuOOH/Ti(O*i*Pr)$_4$ gave the single epoxide **13**[14] in 83% yield.[15] Oxidation of **13** with SeO_2 for 5.5 h gave 43% of deoxyclerocidin (**14**);[16] longer oxidations gave inhomogeneous products.[4] Treatment of **14** with formacetic anhydride gave **15**, which was identical to the rearrangement product obtained by Jacquet from clerocidin and diazomethane.[4] ([α_D](obsd)=+44°, c=0.165, $CHCl_3$, ([α_D](ref.)=+49°, c=0.25, $CHCl_3$, identical NMR spectra; 9.30 ppm, s, 1H; 8.01 ppm, s, 1H; 6.56 ppm, bs, 1H; 5.37 ppm, dd, 1H, J=8.8 Hz, ~2 Hz; 3.05 ppm, AB-system, 2H; HRMS [M+NH_4]$^+$ calcd: 384.2437, obsd: 384.2437).

To avoid the harsh SeO_2 conditions, we coupled aldehyde **11** with 1-TBDPSilyloxy-3-buten-2-one[17] as above to isolate, after $NaIO_4$ oxidation, a 1:4 ratio of **16**[18] and its C(12)-epimer (Scheme 2). Treatment of **16** with *t*-BuOOH/Ti(O*i*Pr)$_4$, followed by *O*-formylation, gave **17** in 74% yield. Desilylation with HF/pyridine gave 90% of the selectively protected tetrahydroclerocidin **18**.[19] Treatment of **18** with Dess–Martin reagent at 0°C gave dihydroclerocidin **19**.[20]



Scheme 2. Reagents and conditions: (a) 1-TBDPSiO-but-3-en-2-one, PhSeTMS, TMSOTf, 10% (12-*R*)+40% (12-*S*); (b) $NaIO_4$; (c) *t*BuOOH, Ti(OiPr)$_4$, MS; (d) AcOCHO, pyr., 79%; (e) HF–pyridine, reversed phase FCC, 90%; (f) 2.4 equiv. Dess–Martin periodinane, 0°C, 5 min, 50%

Subsequent attempts to achieve the final oxidation of the α-hydroxyketone **19** using Dess–Martin reagent led in our hands to intractable mixtures. Our route thus comprises an independent total synthesis of the Jacquet compound, provides synthetic confirmation of absolute configuration in this series, but has not attained access to clerocidin itself.

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6. Compound **5**: ^{1}H NMR ($CDCl_3$, ppm) 4.82 (s, 1H); 4.80 (s, 1H); 4.12 (q, 2H, J=7 Hz); 3.98–3.82 (m, 4H); 2.51 (s, 2H); 2.38 (m, 1H); 2.20 (m, 2H); 1.80–1.35 (m, 8H); 1.26 (t, 3H, J=7 Hz); 1.17 (s, 3H); 1.10 (s, 3H).
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9. Compound **9**: ^{1}H NMR ($CDCl_3$, ppm) 9.32 (s, 1H); 6.58 (m, 1H); 4.12 (AB part of ABX_3 system, 2H) 2.60–2.30 (m, 3H); 2.40 (d, 1H, J=15 Hz); 2.16 (d, 1H, J=15 Hz); 2.00 (m, 2H); 1.70–1.20 (m, 5H); 1.24 (s, 3H); 1.28 (t, X_3 of ABX_3, 2H, J=7 Hz); 1.19 (s, 3H); 1.00 (d, 3H, J=7 Hz). IR (cm^{-1}) 1735, 1695.
10. Compound **11**: ^{1}H NMR ($CDCl_3$, ppm) 9.93 (t, 1H, J=2.5 Hz); 7.70 (m, 4H); 7.50–7.37 (m, 6H); 5.72 (bs, 1H); 4.18 (s, 2H); 2.42–0.85 (m, 10H); 1.20 (s, 3H); 1.06 (s, 12H); 1.00 (d, 3H, J=7 Hz). IR (cm^{-1}) 1725.
11. Oxidation of crude aldol products was necessary to suppress retro-aldol fragmentation.
12. Compound **12**: ^{1}H NMR ($CDCl_3$, ppm) 7.75–7.66 (m, 4H); 7.48–7.36 (m, 6H); 6.12 (s, 1H); 6.04 (s, 1H); 5.68 (bs, 1H); 4.58 (m, 1H); 4.18 (s, 2H); 2.80 (bs, 1H), 2.40 (s, 3H); 2.25–0.80 (m, 15H); 1.06 (s, 12H); 0.98 (s, 3H). HR-MS (DCI) $[M+NH_4]^+$ calcd: 576.3873, obsd: 576.3859
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15. Compound **13**: HRMS (DCI) $[M+NH_4]^+$ calcd: 592.3822, obsd: 592.3831.
16. Compound **14**: ^{1}H NMR ($CDCl_3$, ppm) 9.32 (s, 1H); 6.76 (m, 1H); 3.72 (m, 1H); 3.10 (AB-system, 2H); 2.45–0.85 (m, 13H); 2.13 (s, 3H); 1.25 (s, 3H); 1.05 (s, 3H); 1.04 (d, 3H, J=7 Hz).
17. Prepared from 2-TBDPSilyloxy-*N*-methyl-*N*-methoxy-acetamide, analogous to Nemoto, H.; Shiraki, M.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 10391.
18. Compound **16**: ^{1}H NMR ($CDCl_3$, ppm) 7.70 (d, 8H, J=7 Hz); 7.50–7.37 (m, 12H); 5.85 (s, 1H); 5.81 (s, 1H); 5.66 (bs, 1H); 4.63 (AB-system, 2H); 4.47 (m, 1H); 4.18 (bs, 2H); 2.75 (bs, 1H); 2.25–0.80 (m, 21H); 1.14 (s, 9H); 1.08 (s, 9H). IR: 1685, 1425 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calcd: 835.4554, obsd: 835.4591.
19. Compound **18**: ^{1}H NMR ($CDCl_3$, ppm) 8.05 (s, 1H); 5.55 (bs, 1H); 5.39 (dd, 1H, J=8.9 Hz, 2.8 Hz); 4.28 (AB-system, 2H); 4.15 (s, 2H); 3.18 (d, 1H, J=4.8 Hz); 3.03 (d, 1H, J=4.8 Hz); 2.25–0.85 (m, 14H); 1.18 (s, 3H); 1.07 (s, 3H); 1.03 (d, 3H, J=7.0 Hz). HRMS (DCI) $[M+NH_4]^+$ calcd: 398.2543, obsd: 398.2541.
20. Compound **19**: ^{1}H NMR ($CDCl_3$, ppm) 9.35 (s, 1H); 8.06 (s, 1H); 6.57 (bs, 1H); 5.38 (bd, 1H, J=9 Hz); 4.26 (AB-system, 2H); 3.17 (d, 1H, J=4.7 Hz); 3.01 (d, 1H, J=4.7 Hz); 2.25–0.85 (m, 13H); 1.18 (s, 3H); 1.07 (s, 3H); 1.03 (d, 3H, J=7.0 Hz).