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Anti Aldol Reactions of Lactate-Derived Ketones: Application to the Total Synthesis of (–)-ACRL Toxin IIIB.

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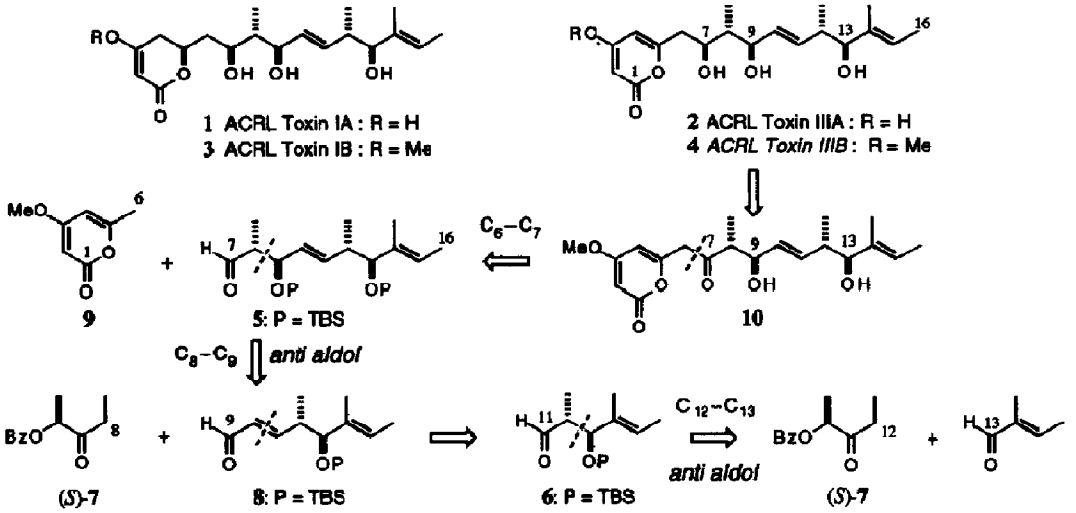
Abstract: The fungal polyketide derivative (–)-ACRL toxin IIIB (**4**) has been prepared in 15 steps (21% yield) from ketone (*S*)-**7** with 88% overall ds. The boron-mediated *anti* aldol reaction of (*S*)-**7** is used twice in the synthesis, controlling the stereochemistry at C_8 / C_9 and C_{12} / C_{13}.

The phytopathogenic fungus *Alternaria citri*, which causes brown spot disease of citrus, produces several host-specific toxins that damage the leaves of rough lemon and Rangpur lime plants.[1] The major component, ACRL toxin IA (**1** in **Scheme 1**), is the most active toxin.[1a] ACRL toxin IIIA (**2**) was isolated in smaller quantities, together with other minor components.[1b] Full structural characterisation of the toxins was only possible from their methyl ether derivatives ACRL toxin IB (**3**) and IIIB (**4**). The stereochemistry of these fungal polyketides was determined by a series of NMR and circular dichroism studies and X-ray crystallography performed on a derivative of **1**.[1c] We now report an efficient asymmetric synthesis[2] of (–)-ACRL toxin IIIB (**4**), which proceeds with a high level of stereocontrol (88% overall diastereoselectivity), using recently developed aldol chemistry from our laboratory.

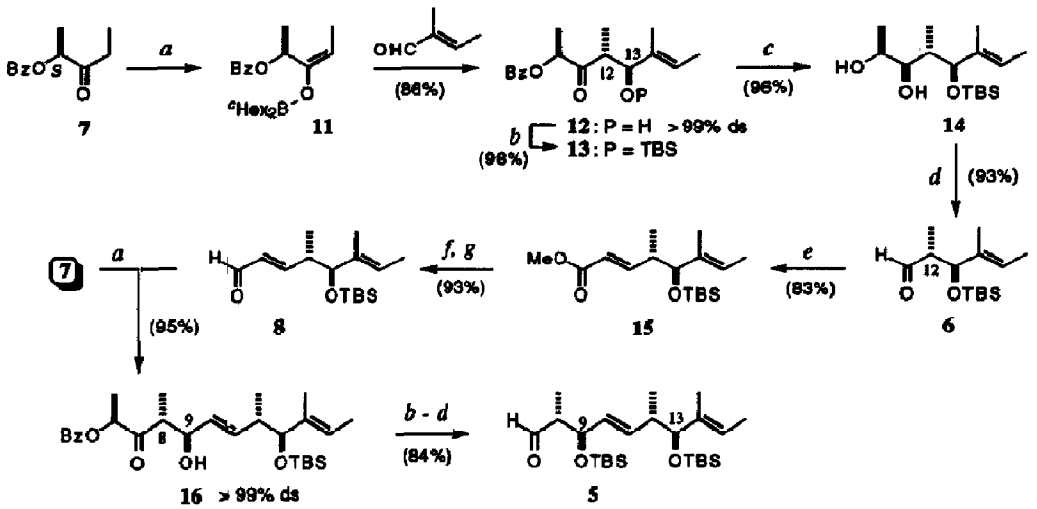


Scheme 1

We were attracted to ACRL toxin IIIB (**4**) as a synthetic target due to the two *anti* configured propionate units of the side-chain, which are usually more difficult to control by conventional aldol methodology than the corresponding *syn* relationships.[3] As shown in **Scheme 1**, our retrosynthetic analysis is based on two key aldol disconnections at C_8–C_9 in **5** and C_{12}–C_{13} in **6**. We have already shown that the *E*-enol borinate from the lactate-derived ketone (*S*)-**7** is an effective chiral propionate reagent for *anti* aldol additions to both achiral and

chiral aldehydes,[4a] and that the products can be manipulated to give a range of synthetically useful intermediates.[4b] By using the *anti* aldol reaction of (*S*)-**7** twice, a high level of stereocontrol in the construction of aldehydes **5** (from **8**) and **6** (from tiglic aldehyde) should result. The final coupling, planned between **5** and the α-pyrone **9**, has some precedent in a previous synthesis of ACRL toxin IIIB by Mulzer *et al.*[2a] However, to achieve efficient stereocontrol at C_7, we elected to explore the reduction of ketone **10**. Our synthesis of (–)-ACRL toxin IIIB, which proceeded along these lines, is summarised in **Schemes 2** and **3** and outlined below.

The synthesis of the aldehyde **5**, with silyl-protected hydroxyls at C_9 and C_{13}, is described first (**Scheme 2**). The two stereocentres at C_{12} and C_{13} were simultaneously introduced by a boron-mediated *anti* aldol reaction between ethyl ketone (*S*)–**7** and tiglic aldehyde (*E*-2-methyl-2-butenal). This reaction proceeded with excellent diastereoselectivity (>99% ds) using our standard conditions.[4a] Thus ketone **7** was enolised by $^c Hex_2BCl$ / Me_2NEt in Et_2O, to generate the *E*-enol borinate **11**, followed by addition of the aldehyde. This led to isolation of the pure *anti* aldol isomer **12**,[5] $[\alpha]_D^{20} = +28.1°$ (*c* 1.8, $CHCl_3$), in 86% yield after a single recrystallisation (m.p. 92–94 °C, Et_2O–hexane). HPLC analysis of the crude aldol product indicated that less than 1% of other isomers were produced.



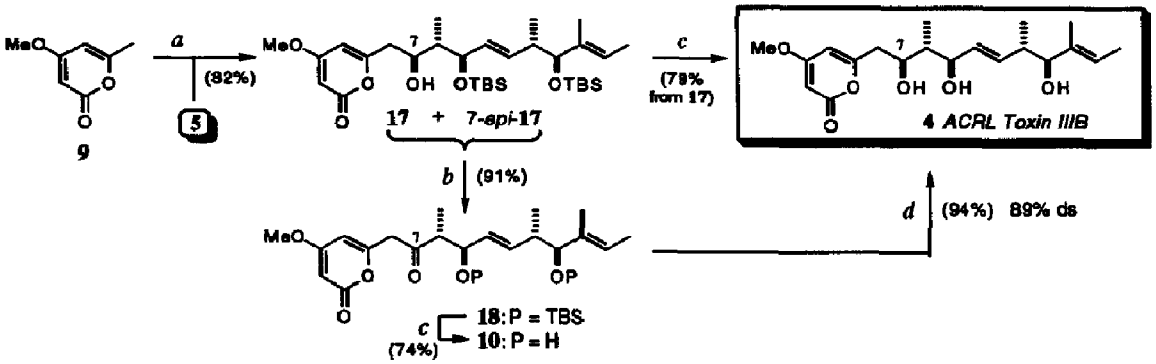
Scheme 2 (*a*) $^c Hex_2BCl$, Me_2NEt, Et_2O, 0 °C, 2 h; tiglic aldehyde (for **12**) or **8** (for **16**), –78 → –16 °C, 16 h; H_2O_2, MeOH, pH7 buffer; (*b*) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 1 h; (*c*) $LiBH_4$, THF, –78 → 20 °C, 16 h; (*d*) $NaIO_4$, MeOH, H_2O, 20 °C, 1 h; (*e*) $(MeO)_2P(=O)CH_2CO_2Me$, $Ba(OH)_2$, THF : H_2O (40 : 1), 20 °C, 16 h; (*f*) DIBAL, Et_2O, –40 °C, 2 h; (*g*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 1 h.

Following our previous work,[4b] the β-hydroxy ketone **12** was efficiently converted into aldehyde **6** in 88% overall yield by the three-step sequence: (*i*) silyl protection by $^t BuMe_2SiOTf$ to give **13**; (*ii*) $LiBH_4$ reduction to give the corresponding diol **14** (90% ds); (*iii*) oxidative glycol cleavage by $NaIO_4$ to generate **6**, $[\alpha]_D^{20} = +30.6°$ (*c* 1.7, $CHCl_3$). Next, chain extension by a barium hydroxide promoted Horner-Wadsworth-Emmons reaction[6] gave solely the *E*-alkene **15** in 83% yield. The use of stronger bases, *e.g.* $^n BuLi$, in this reaction led to substantial epimerisation at C_{12}. Subsequent DIBAL reduction of **15** to the allylic alcohol, followed by Dess-Martin oxidation,[7] gave enal **8**, $[\alpha]_D^{20} = -19.2°$ (*c* 2.5, $CHCl_3$), in 93% yield.

The two stereocentres at C_8 and C_9 were introduced in an analogous manner to that used to introduce those at C_{12} and C_{13}. Thus a boron-mediated aldol reaction between (*S*)-**7** and **8**, under the standard reaction

conditions,[4a] proceeded in a gratifying 95% yield to give the desired *anti* aldol isomer **16**,[5] $[\alpha]_D^{20}$ = +4.2° (*c* 0.9, $CHCl_3$). Again, HPLC and NMR analysis indicated > 99% diastereoselectivity for this aldol addition. Finally, repeating the same three-step sequence[4b] on **16**, as used earlier for **12** → **6**, gave the required aldehyde **5**, $[\alpha]_D^{20}$ = –33.6° (*c* 2.2, $CHCl_3$), in 84% overall yield. This aldol-based synthesis of the ACRL toxin side-chain is notable for achieving essentially complete stereocontrol at the four new stereocentres and proceeds in 46% yield from ketone (*S*)-**7**.

As shown in **Scheme 3**, the completion of our ACRL toxin IIIB synthesis required a coupling between chiral aldehyde **5** and the commercially available α-pyrone **9**. Ideally, this should be accompanied by control of the configuration at the new C_7 stereocentre, which is in the opposite sense to that expected by Felkin-Anh selectivity from **5**. A similar coupling reaction was used in the Mulzer synthesis,[2a] which gave a 96 : 4 mixture in favour of the required stereochemistry at C_7, after protecting group removal.[8] In our case, addition of the aldehyde **5** to the metallated α-pyrone **9** (KHMDS, Et_2O, –100 °C) resulted in at best a 73 : 27 ratio[8] of adducts (82%), with the major product being the desired (anti-Felkin) alcohol **17**. To resolve the problem of modest stereocontrol encountered in setting up the C_7 stereocentre, we examined reduction of the corresponding unprotected ketone **10**. This was readily obtained in 67% yield by Dess-Martin oxidation of the mixture of **17** and 7-*epi*-**17** and treatment of **18** with HF•pyridine complex. Reduction of the β-hydroxyketone **10** by $LiBH_4$,[9a] *via* the *in situ* generated dibutylboron chelate,[9] gave (–)-ACRL toxin IIIB (**4**) and its C_7-epimer with 89% diastereoselectivity.[10] A single recrystallisation gave an 82% yield of isomerically pure **4**, m.p. 153–155 °C (EtOAc), which had ^1H and ^{13}C NMR data[5] in full agreement with that reported for the authentic compound.[1b] The specific rotation recorded for **4**, $[\alpha]_D^{20}$ = –47.0° (*c* 0.6, $CHCl_3$), was in good agreement with that obtained by Professor Mulzer, $[\alpha]_D^{20}$ = –49.0° (*c* 0.8, $CHCl_3$).[8] A shorter, but less selective, synthesis of **4** was also achieved by chromatographic separation of **17** from its C_7-epimer[11] and deprotection.



Scheme 3 (*a*) $KN(SiMe_3)_2$, Et_2O, –100 °C, 1 h; **5**, –100 °C, 2 h; (*b*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 1 h; (*c*) HF•pyridine, THF, 0 → 20 °C, 2 h; (*d*) $^nBu_2BOMe$, THF/MeOH, –78 °C, 20 min; $LiBH_4$, 2 h; H_2O_2, pH7 buffer, 1 h.

In conclusion, (–)-ACRL toxin IIIB has been synthesised in 15 steps with 21% overall yield starting from ketone (*S*)-**7** and tiglic aldehyde. The synthesis is characterised by high overall diastereoselectivity (88% ds) as a result of: (*i*) the efficiency of the *anti* aldol reactions of (*S*)-**7** in introducing the C_8/C_9 and C_{12}/C_{13} stereocentres; (*ii*) good control of the C_7 stereocentre in the final reduction step, **10** → **4**.

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1. (a) Gardner, J. M.; Kono, Y.; Tatum, J. H.; Suzuki, Y.; Takeuchi, S. *Phytochemistry* **1985**, *24*, 2861. (b) Kono, Y.; Gardner, J. M.; Suzuki, Y.; Takeuchi, S. *Phytochemistry* **1985**, *24*, 2869. (c) Kono, Y.; Gardner, J. M.; Kobayashi, K.; Suzuki, Y.; Takeuchi, S.; Sakurai, T. *Phytochemistry* **1986**, *25*, 69.

2. For other synthetic work see: (a) ACRL toxin IIIB: Mulzer, J.; Dupre, S.; Buschmann, J.; Luger, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1452; (b) ACRL toxin IB: Lichtenhaler, F. W.; Dinges, J.; Fukuda, Y. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1339.

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5. All new compounds gave spectroscopic data in agreement with the assigned structures. **12** had ^{1}H NMR δ(400 MHz, $CDCl_3$) 8.02 (2H, d, J = 7.5 Hz), 7.55 (1H, t, J = 7.5 Hz), 7.45 (2H, t, J = 7.5 Hz), 5.50 (1H, q, J = 6.7 Hz), 5.43 (1H, dq, J = 1.0, 7.0 Hz), 4.18 (1H, dd, J = 3.2, 9.2 Hz), 3.03 (1H, dq, J = 9.2, 7.0 Hz), 2.00 (1H, d, J = 3.2 Hz), 1.60 (3H, d, J = 6.7 Hz), 1.58 (3H, d, J = 1 Hz), 1.56 (3H, d, J = 7.0 Hz), 1.02 (3H, d, J = 7.0 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 211.2, 166.1, 135.1, 133.3, 129.8, 129.6, 128.4, 124.1, 80.1, 75.1, 45.6, 15.6, 14.5, 13.1, 10.4; HRMS (CI, NH_3) $[M + NH_4]^+$ found 308.1862, $C_{17}H_{26}O_4N$ requires 308.1862. **16** had ^{1}H NMR δ(400 MHz, $CDCl_3$) 8.02 (2H, d, J = 7.4 Hz), 7.56 (1H, t, J = 7.4 Hz), 7.43 (2H, t, J = 7.4 Hz), 5.76 (1H, dd, J = 7.1, 15.5 Hz), 5.42 (1H, q, J = 7.0 Hz) 5.36 (1H, dd, J = 15.5, 7.9 Hz), 5.31 (1H, q, J = 6.6 Hz), 4.20 (1H, m), 3.61 (1H, d, J = 7.7 Hz), 2.87 (1H, dq, J = 8.4, 7.1 Hz), 2.27 (1H, m), 1.97 (1H, d, J = 3.1 Hz), 1.56 (3H, d, J = 6.6 Hz), 1.55 (3H, d, J = 7.0 Hz), 1.50 (3H, s), 1.12 (3H, d, J = 7.1 Hz), 0.83 (9H, s), 0.80 (3H, d, J = 6.9 Hz), -0.04 (3H, s), -0.09 (3H, s); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 210.9, 165.2, 138.3, 136.6, 133.2, 129.8, 129.4, 129.1, 128.4, 121.4, 83.0, 75.5, 75.0, 48.2, 40.6, 25.8, 18.2, 16.7, 15.5, 14.5, 12.8, 11.0, -4.7, -5.1; HRMS (+FAB) $[M - H]^+$ found 487.2863, $C_{28}H_{43}O_5Si$ requires 487.2880. **4** had ^{1}H NMR δ(400 MHz, $CDCl_3$) 5.94 (1H, d, J = 2.1 Hz), 5.61 (1H, m), 5.57 (1H, m, J = 15.9, 7.9 Hz), 5.41 (1H, d, J = 2.1 Hz), 5.46 (1H, q, J = 7.2 Hz), 4.09 (1H, m), 4.07 (1H, m), 3.78 (3H, s), 3.65 (1H, d, J = 6.9 Hz), 2.80 (1H, dd, J = 2.2, 14.8 Hz), 2.47 (1H, dd, J = 9.4, 14.8 Hz), 2.32 (1H, m), 1.71 (1H, m), 1.63 (3H, d, J = 6.9 Hz), 1.58 (3H, s), 0.85 (3H, d, J = 6.9 Hz), 0.84 (3H, d, J = 6.8 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 171.4, 165.2, 163.2, 136.5, 135.9, 132.8, 123.3, 101.9, 87.8, 82.3, 77.9, 72.7, 55.8, 43.4, 40.4, 39.4, 17.2, 13.4, 13.1, 10.5; HRMS (+FAB) $[M + H]^+$ found 367.2121, $C_{20}H_{31}O_6$ requires 367.2121.

6. Paterson, I.; Yeung, K-S.; Smaill J. B. *Synlett*, **1993**, 774.

7. Dess, D. D.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

8. Professor Mulzer has pointed out to us that the 96 : 4 ratio reported (ref 2a) is not the ratio of C_7 alcohols from addition to the aldehyde, but represents the ratio obtained after the subsequent deprotection steps. Selective destruction of the minor isomer apparently occurs under the deprotection conditions. The kinetic selectivity actually obtained is similar to that which we observe, *i.e.* up to 80 : 20 in favour of the required C_7 isomer. Mulzer, J. *personal communication*.

9. (a) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A.; Yeung, K.-S. *Tetrahedron Lett.* **1994**, *35*, 3405. (b) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (c) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

10. In comparison, reduction of **10** with catechol borane also gave **4** preferentially, but with lower stereoselectivity (75% ds): Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.

11. The minor alcohol 7-*epi*-**17** could be converted *via* Dess-Martin oxidation and DIBAL reduction (under Felkin-Anh control) to give more of the required isomer **17**.

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