Communications

Total Synthesis of ACRL Toxin IIIb: A Protocol for Parlaying Aldols into Synthons Containing Three Stereocenters Having an [*n*, *n* + 1, *n* + 4] Relationship

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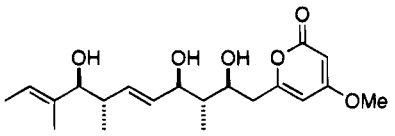
Summary: ACRL toxin IIIb (**1**) has been prepared by total synthesis. The synthesis demonstrates a general strategy for preparing compounds containing three stereocenters having an [*n*, *n* + 1, *n* + 4] relationship.

The phytopathogenic fungus, *Alternaria citri*, a causal agent of brown spot disease of Rough lemons and Rangpur limes, produces several host specific toxins, called the ACRL toxins I-IV.[1] Because the natural toxins are unstable, they have been characterized as the pyrone methyl ethers, which are known as ACRL toxins Ib, IIb, IIIb, and IVb. In this paper, we report a total synthesis of ACRL toxin IIIb (**1**).[2]



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The synthesis began with the known β-*tert*-butylthioacrolein (**2**),[3,4] which was converted by the Evans protocol[5] into aldol **3**.[6] The chiral auxiliary was removed by successive treatment of **3** with lithium benzyloxide and diisobutylaluminum hydride. The primary hydroxy group of diol **4** was selectively tritylated and the resulting hydroxy ether acylated with propionic anhydride to obtain **5**. This allyl ester was subjected to conditions of the Ireland ester enolate Claisen rearrangement[7] to obtain carboxylic acid **6** in excellent yield.[8] Treatment of acid **6** with *N*,*N*-carbonyldiimidazole and *N*-methoxymethylamine gave the Weinreb amide, which was treated at low temperature with (*E*)-2-lithio-2-butene, prepared by metalation of (*E*)-2-bromo-2-butene[9] with *tert*-butyllithium in ether. The resulting enone (**7**) was reduced with sodium borohydride in the presence of cerium(III) chloride to obtain alcohol **8** as an 8:1 mixture of diastereomers (only the major isomer is shown in Scheme 1). Allyl sulfide **8** was oxidized by *m*-chloroperoxybenzoic acid to the sulfoxide, which was treated with trimethyl phosphite in methanol to obtain **9**, having four of the five stereocenters of ACRL toxin III.[10] The two secondary hydroxy groups were protected as *tert*-butyldimethylsilyl ethers, and the trityl group was removed by reaction with zinc bromide in methylene chloride[11] to obtain **10**, which was oxidized to aldehyde **11** by the Dess–Martin procedure.[12]

To add the α-pyrone ring of the ACRL toxins, we employed the tetrahydropyranyl ether of 4-hydroxy-6-methyl-2-pyrone (**12**).[13] Treatment of **12** with LDA in THF–HMPA, followed by addition of aldehyde **11**, provided a 1:1 mixture of diastereomeric alcohols (**13**). This material was oxidized by the Dess–Martin procedure to a homogeneous ketone (**14**). Attempts to reduce **14** with L-Selectride resulted only in deprotonation of the acidic

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(1) (a) Kono, Y.; Gardner, J. M.; Suziki, Y.; Takeuchi, S. *Phytochemistry* **1985**, *24*, 2869. (b) Kono, Y.; Gardner, J. M.; Kobayshi, S.; Sakuri, T. *Phytochemistry* **1986**, *25*, 69. (c) Kono, Y.; Gardner, J. M.; Tatum, J. H.; Suziki, Y.; Takeuchi, S. *Phytochemistry* **1988**, *53*, 1922.

(2) For previous synthetic work in this area, see: (a) Lichtenthaler, F. W.; Dinges, J.; Fukuda, Y. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1339. (b) Mulzer, J.; Dupre, S.; Buschmann, J.; Luger, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1452.

(3) (a) Julia, S.; Lefebvre, C. *Tetrahedron Lett.* **1984**, *25*, 189. (b) Julia, S.; Reglier, S.; Ruel, O.; Lorne, R. *Synthesis* **1983**, 624. (c) Ruel, O.; Guitlet, E.; Julia, S. *Tetrahedron Lett.* **1983**, *24*, 61.

(4) The original Julia synthesis of **2** was modified by use of PDC in DMF instead of $Ba(MnO_4)_2$ to oxidize the precursor alcohol.

(5) Evans, D. A.; Mathre, D. J.; Ennis, M. D. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(6) The conventional workup procedure for this process, which involves treatment of the crude boron aldolate with H_2O_2, gave low yields, presumably because of oxidation at sulfur. The indicated yield was obtained by treating the aldolate with pH 7 buffer at −78 °C, followed by a normal aqueous workup.

(7) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Org. Chem. Soc.* **1976**, *41*, 986. (b) Ireland, R. E.; Mueller, R.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem. Soc.* **1991**, *56*, 650.

(8) A curious phenomenon was observed in this rearrangement. The normal protocol for the Ireland ester enolate Claisen rearrangment is to treat the ester with LDA in THF at −78 °C, add a solution of *tert*-butyldimethylsilyl chloride in HMPA at −78 °C, and finally warm the solution to 65 °C. When **5** was treated in this manner, we obtained the silyl ketene acetal, but very little of the desired acid **6**. However, TLC analysis showed that allowing the material that had been withdrawn for the analysis to sit on the bench top for a few minutes resulted in a dramatic change in composition. If the sample was allowed to sit open to the air for a longer period of time, less of the silyl ketene acetal was observed and more acid was produced. To further test this, an aliquot of the reaction was removed and left open to the air. The same pattern was observed; the higher R_f spot (silyl ketene acetal) slowly disappeared and the lower R_f spot appeared. The reason for the observed phenomenon is unknown. It may be that exposure to air causes hydrolysis of the silyl ketene acetal to the the ester enolate, which is the species actually undergoing the rearrangement. Another possible explanation is that evaporation of THF and hexane increases the solvent polarity, resulting in a conformational change in the substrate that promotes rearrangement.

(9) This alkene was prepared in 60% yield by successive treatment of 2-butyne with Cp_2ZrHCl and *N*-bromosuccinimide: Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(10) Although **8** is a mixture of diastereomeric sulfoxides, only one diastereomer of **9** can be detected by ^1H NMR or ^{13}C NMR spectroscopy. This is, of course, to be expected, since both diastereomeric sulfoxides should rearrange suprafacially.

(11) Kohli, V.; Blöcker, H.; Köster, H. *Tetrahedron Lett. 21*, **1980**, 2683.

(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(13) This compound was prepared by treatment of the commercially-available 4-hydroxy-6-methyl-2-pyrone with dihydropyran and pyridinium *p*-toluenesulfonate in CH_2Cl_2.

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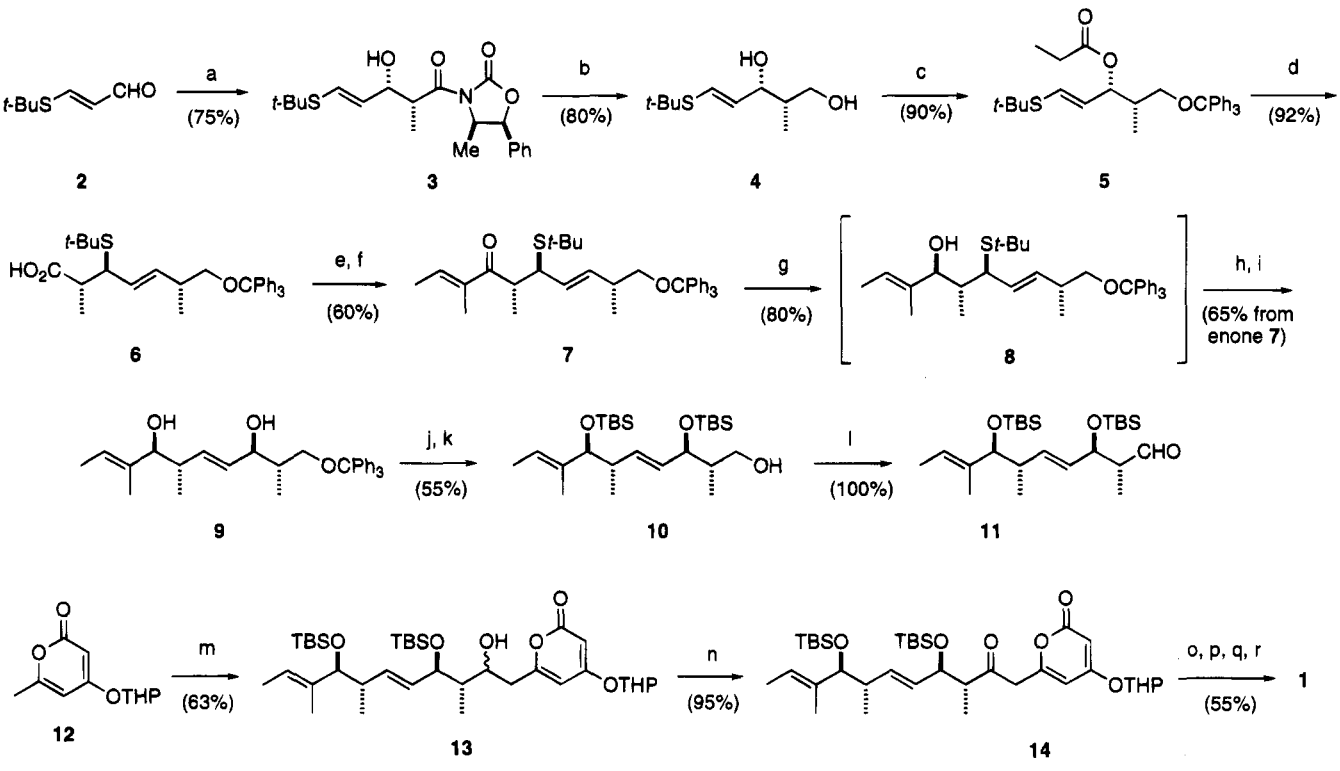
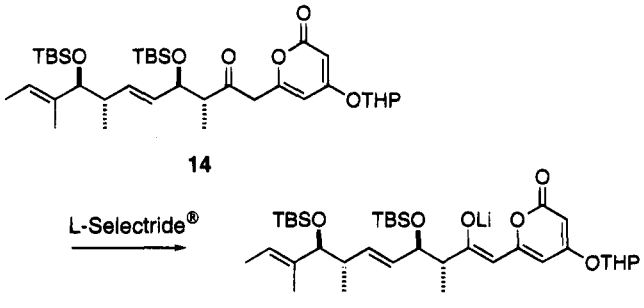
Scheme 1[a]



[a] (a) *N*-propionyloxazolidone derived from (1*S*,2*R*)-(+)-norephedrine, Bu_2OTf, $Et(i\text{-}Pr)_2N$, CH_2Cl_2; (b) (i) $PhCH_2OLi$, THF, 0 °C, (ii) DIBAL, −78 °C; (c) (i) Ph_3CCl, DMAP, Et_3N, CH_2Cl_2, (ii) $(CH_3CH_2CO)_2O$; (d) (i) LDA, THF, −78 °C, (ii) TBSCl, HMPA, (iii) −78 °C → 65 °C; (e) *N*,*N*-carbonyldiimidazole, MeONHMe·HCl; (f) (*E*)-2-lithio-2-butene, ether, −78 °C → −40 °C; (g) $NaBH_4$, $CeCl_3$, DMSO; (h) *m*-CPBA, CH_2Cl_2, −78 °C; (i) $P(OMe)_3$, MeOH; (j) TBDMSOTf, Et_3N, CH_2Cl_2, −78 °C; (k) $ZnBr_2$, CH_2Cl_2; (l) $SO_3{\cdot}C_5H_5N$, Et_3N, DMSO, CH_2Cl_2; (m) LDA, HMPA, **11**; (n) Dess–Martin, CH_2Cl_2; (o) 8:8:1 HOAc, THF, H_2O; (p) L-Selectride; (q) CH_2N_2, ether; (r) $HF{\cdot}C_5H_5N$, THF.

position between the carbonyl group and pyrone ring:



This problem was solved by removal of the THP group, which was accomplished by treatment of **14** with aqueous acetic acid. Reduction of the resulting deprotected compound provided two diastereomeric alcohols in a ratio of 5:1. Methylation of the pyrone hydroxy group and removal of the *tert*-butyldimethylsilyl groups gave compound **1** in 55% overall yield from ketone **14**. The synthetic ACRL toxin IIIb was identified by comparison with an authentic sample kindly provided by Dr. Kono.

The synthesis of **1** reported here requires 16 steps and proceeds with an overall yield of approximately 4%. More importantly, the synthesis illustrates a basic strategy for preparing compounds containing three stereocenters that have a [*n*, *n* + 1, *n* + 4] relationship (e.g., **9**). The technique should be general for preparing such synthons with any stereochemistry desired, since one can begin with either a syn or anti aldol (of either chirality) and employ either the *E* or *Z* enolate in the Ireland ester enolate Claisen rearrangement.

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Supplementary Material Available: Experimental procedures and analytical data for all new compounds reported in this paper (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.