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Total Synthesis of Phenalamide A_2

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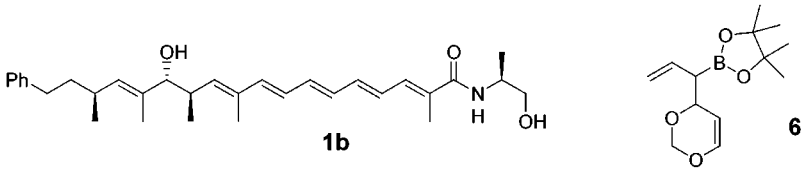
ABSTRACT



Phenalamide A_2 (1b) has been synthesized for the first time. The synthesis features the homologation of aldehyde 5 to trienal 3 with the new conjunctive reagent 6 and the formation of amide 14 with the functionalized Horner–Emmons reagent 4.

The myxalamides[1] **2** and the phenalamides[2] (stipiamides[3]) (**1**) belong to a class of natural products isolated from gliding bacteria (Figure 1). These compounds attract attention because of antibiotic, antifungal, and antiviral activity, as well as being agents to reverse multidrug resistance phenomena. A first synthesis of phenalamide A_1 (= stipiamide) (**1a**) has been reported by M. B. Andrus in 1997[4] followed by a synthesis of myxalamide A by C. H. Heathcock in 1999.[5] The Andrus group has expanded their route to access a series of analogues of the phenalamides.[6] In addition, the group of D. A. Whiting has come up with a concise synthon approach to the main chain of the myxalamides.[7]

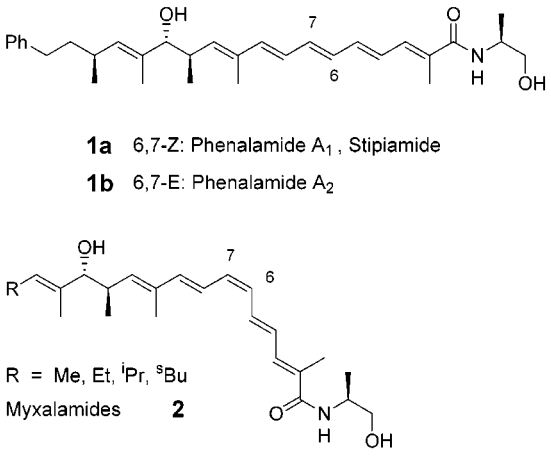
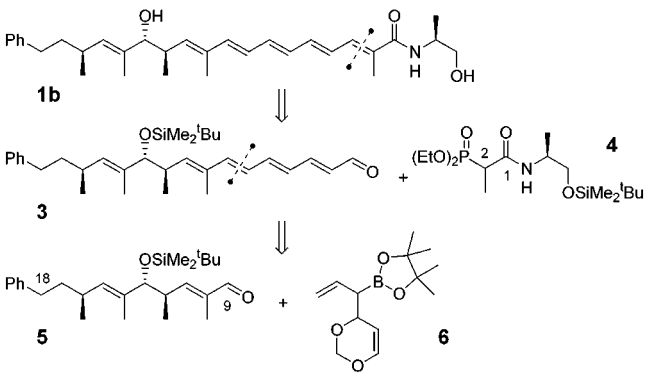


Figure 1. Myxalamides and phenalamides.

The nature of approaches depends on whether a C-6/C-7 *Z*- or C-6/C-7 *E*-double bond is targeted. We envisaged and realized a convergent route to phenalamide A_2, with the C-6/C-7 *E*-configuration.

Key to our approach was the novel conjunctive reagent **6**, by which C-9−C-18 enal **5** can be homologated to tetraenal **3** and subsequently joined to C-1/C-2 amide building block **4** (Scheme 1). The homologation process is effected by an

Scheme 1



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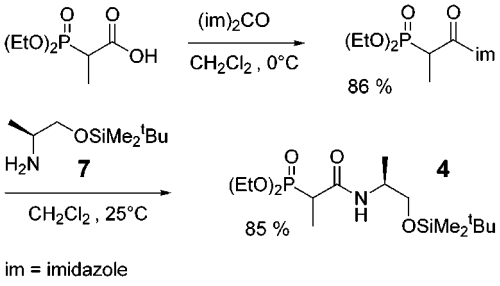
allylboration reaction of the aldehyde **5** followed by a cycloreversion of the dioxene ring.

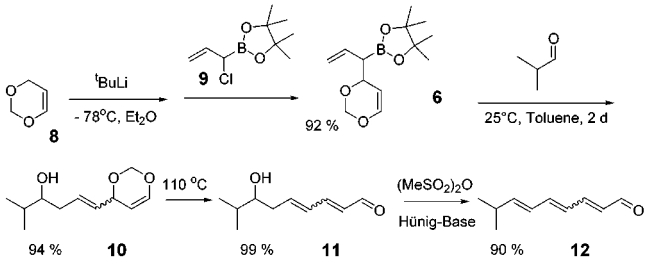
The requisite enantiomerically pure enal **5** was prepared by a route[8] which is equivalent to the one used by Andrus.[4] The other component, the C-1/C-2 amide **4**, was generated in a simple manner from monoprotected alaninol **7** (Scheme 2).

Scheme 2



The novel conjunctive reagent **6** was obtained from 1,3-dioxene **8**[9] by lithiation[10] followed by alkylation with α-chloroallyl boronate **9**[11] (Scheme 3).

Scheme 3

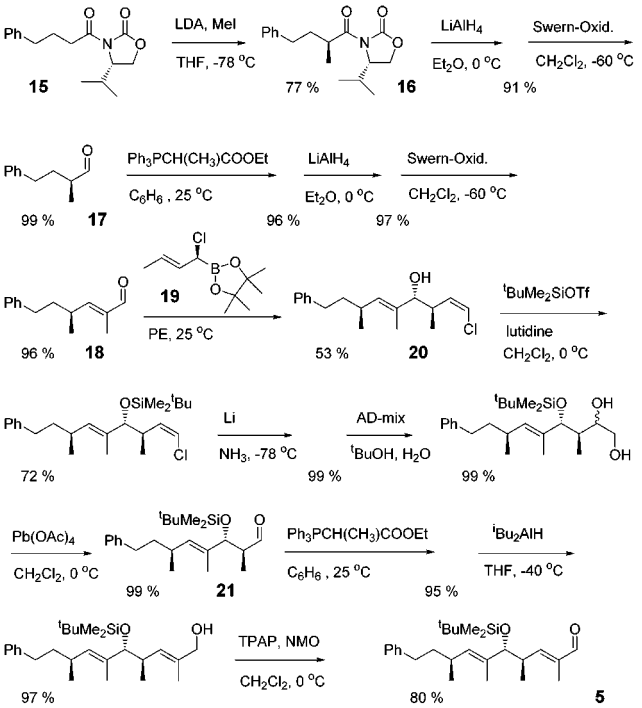


Racemic reagent **6** is a mixture of diastereomers, which need not be separated in the present context. Reaction of **6** with aldehydes, e.g., isobutyraldehyde at room temperature, furnished adducts **10** as a 2:1 mixture of *E*/*Z*-isomers (determined by NMR). Subsequent heating of **10** to 110 °C generated hydroxydienal **11** by cycloreversion of the dioxene ring.[10] Addition of a catalytic amount of iodine equilibrated the mixture toward the *E*-isomer (*E*/*Z*-ratio > 20:1, determined by NMR). This reaction sequence can be conveniently carried out in toluene as solvent as a one-pot procedure giving, e.g., **11** in 90−93% yield.

Conversion of **11** to trienal **12** requires the elimination of water. To this end, brief treatment of **11** with methanesulfonic anhydride and ethyldiisopropylamine in dichloromethane furnished 90% of tetraenal **12**. This reaction sequence was then applied to aldehyde **5** in order to effect the synthesis of phenalamide A_2 (**1b**) (Scheme 4).

Reaction of enal **5** with conjunctive reagent **6** including a treatment with iodine furnished 69% of alcohol **13** as a 9:1 mixture of *E*/*Z*-isomers, from which the labile polyenal **3** (6,7-*E*/6,7-*Z* = 9:1) could be obtained in 85% yield. This

(8) Synthesis of aldehyde **5** started from oxazolidinone **15**, which was alkylated to give **16**, followed by transformation into aldehyde **17**. Standard homologation led to aldehyde **18**. We used the enantiomerically pure α-chlorocrotylboronate **19**[12] to create the two new stereogenic centers in **20** with reagent control of diastereoselectivity.[13] Alcohol **20** was obtained diastereomerically pure. Even if the asymmetric induction was not complete, the few percent of the diastereomeric byproduct could be easily identified and separated on account of the *E*-chlorovinyl unit as opposed to the *Z*-chlorovinyl unit of desired product **20**. The use of chloroboronate **19** entailed an additional step to remove the chlorine atom. This was effected after silylation of the alcohol by reduction with lithium in liquid ammonia.[14] Selective oxidative cleavage of the terminal double bond followed the precedent set by Andrus.[15] Aldehyde **21** obtained was again homologated in a standard fashion to give the key aldehyde **5**.



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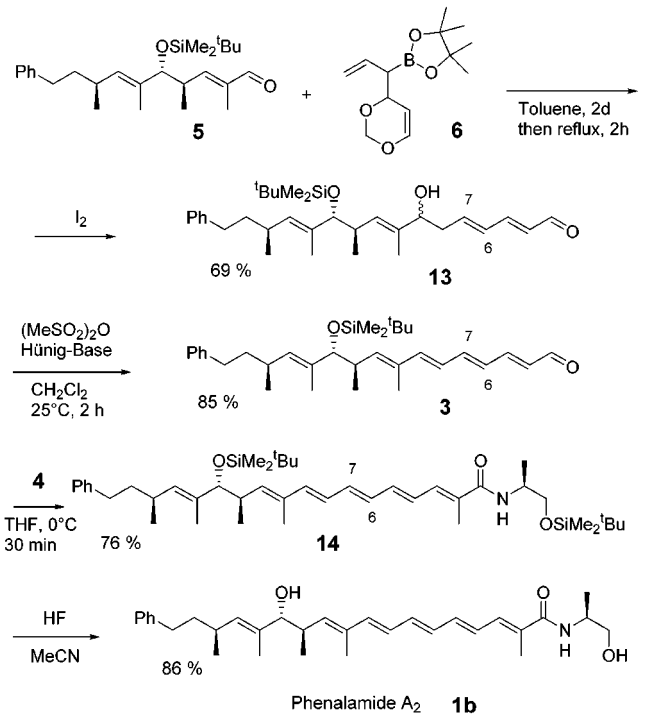
Scheme 4



was immediately condensed with phosphonate **4** to give bis-protected phenalamide **14** (76%). All the operations onward from **5** were carried out with essentially complete exclusion of light, to avoid *E*/*Z*-isomerization of the polyene system. Thus, at the stage of **14** the material was ≥ 90% *all-E*. Phenalamide A_2 (**1b**) was ultimately liberated in 86% yield by treatment with HF in acetonitrile at 0 °C.

When the 500 MHz NMR spectrum of the product obtained was compared with data published by Höfle,[2] we noted that due to a brief thermal exposure on measuring the NMR spectrum the obtained phenalamide was admixed with ca. 40% of other double bond isomers, among which was phenalamide A_1 to ca. 20%. To substantiate this assignment, the iodine treatment after adding allylboronate **6** to aldehyde **5** was omitted in a complementary reaction sequence. This allowed hydroxydienal **13** (6,7-*E*/6,7-*Z* = 2:1) to be carried through as an *E*/*Z*-isomeric mixture. This reaction sequence resulted eventually in a 4:1 mixture of phenalamide A_2 and the C-6/C-7-*Z* isomeric phenalamide A_1.

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Supporting Information Available: Experimental procedures and full characterization for compounds **1b**, **3**, **4**, **7**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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