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Synthesis of an analog of mycothiazole and total synthesis of pseudotrienic acid B*

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Abstract: An analog of mycothiazole and pseudotrienic acid B were synthesized efficiently by using ring-closing metathesis or cross-metathesis as key reactions.

Keywords: natural products; total synthesis; ring-closing metathesis; cross-metathesis; crotyltitanation.

INTRODUCTION

Over the past few years, natural products have continued to be of interest owing to their wide spectrum of biological and pharmaceutical properties. However, the natural supply of these compounds is usually extremely scarce and full biological evaluation cannot be achieved, thus necessitating synthetic efforts to provide sustainable material. For our part, we have been interested in the synthesis of an analog of mycothiazole and in the total synthesis of pseudotrienic acid B.

MYCOTHIAZOLE AND ANALOGS

Mycothiazole was first isolated in 1988 from the marine sponge *Spongia mycofijiensis* collected from the Vanuatu islands [1], and this compound was also detected in the extracts of another marine sponge of the genus *Dactylospongia* [2]. Mycothiazole was found to exhibit an antihelminthic activity in vitro as well as a rather selective toxicity against a small-cell lung cancer line [1,3]. The structure of mycothiazole was initially established by the analysis of its NMR and high-resolution electron impact mass spectrometry (HREIMS) spectra [1]. However, a revised structure for mycothiazole was recently published on the basis of nuclear Overhauser effect (NOE) experiments and analysis of a higher-field ^{1}H NMR spectrum (600 MHz) [4]. The only difference between the previous and the revised structure lies in the configuration of the C15–C16 disubstituted double bond that is actually (*Z*) in mycothiazole (Fig. 1). As we were involved in the synthesis of mycothiazole before revision of its structure, we have achieved the synthesis of compound **I**, which corresponds to the originally proposed structure of this natural product. We have to point out that one synthesis of compound **I** was previously reported in 2000 [5].

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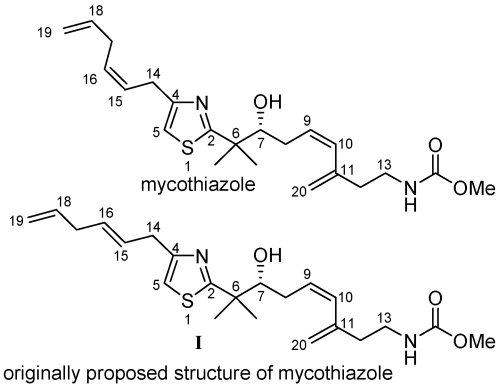
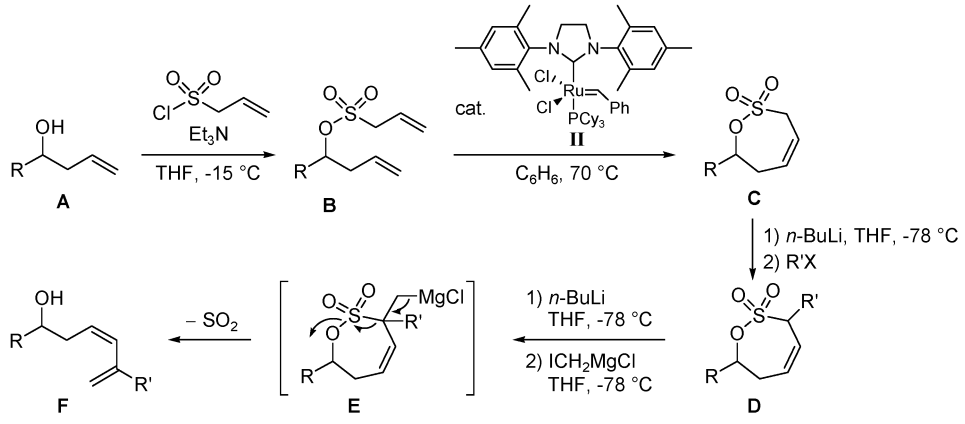


Fig. 1

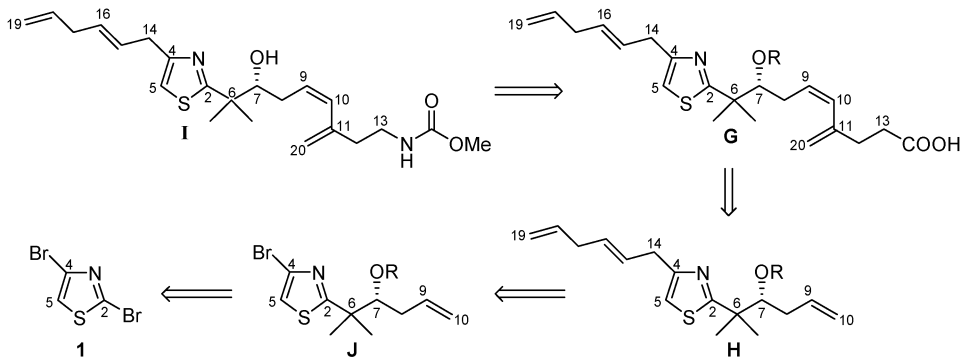
Compound **I** is constituted by a central 2,4-disubstituted thiazole. A 2,5-hexadienyl side chain substitutes the C4 position of the heterocycle, whereas the side chain at C2 includes a nitrogen substituent at C13 (methyl carbamate), a *gem*-dimethyl-substituted carbon (C6) and a homoallylic conjugated (*Z*)-dienol subunit (C7 to C11–C20) with the (*R*) absolute configuration at C7.

The homoallylic conjugated (*Z*)-dienol subunit is a remarkable structural feature of mycothiazole, which is also encountered in other biologically active natural products. Therefore, a methodology was developed to synthesize such subunits from readily available homoallylic alcohols through the intermediacy of unsaturated sultones. Thus, when a homoallylic alcohol of type **A** was treated with allylsulfonyl chloride (Et_3N, tetrahydrofuran (THF), –15 °C), the corresponding unsaturated sulfonate of type **B** was formed and subsequently underwent ring-closing metathesis by treatment with Grubbs second-generation catalyst **II** [6] (C_6H_6, 70 °C) to afford the corresponding unsaturated sultone **C** in good yield [7–10]. The sultone could be alkylated at the α-position of the sulfonyl group (*n*-BuLi, THF, –78 °C then R'X) and the resulting alkylated sultone **D** was metalated (*n*-BuLi, THF, –78 °C) to produce an organolithium reagent which was treated with ICH_2MgCl [11]. The Grignard reagent **E** generated by this operation underwent β-elimination and loss of the sulfur dioxide to deliver the homoallylic conjugated (*Z*)-dienol of type **F** (Scheme 1).



Scheme 1

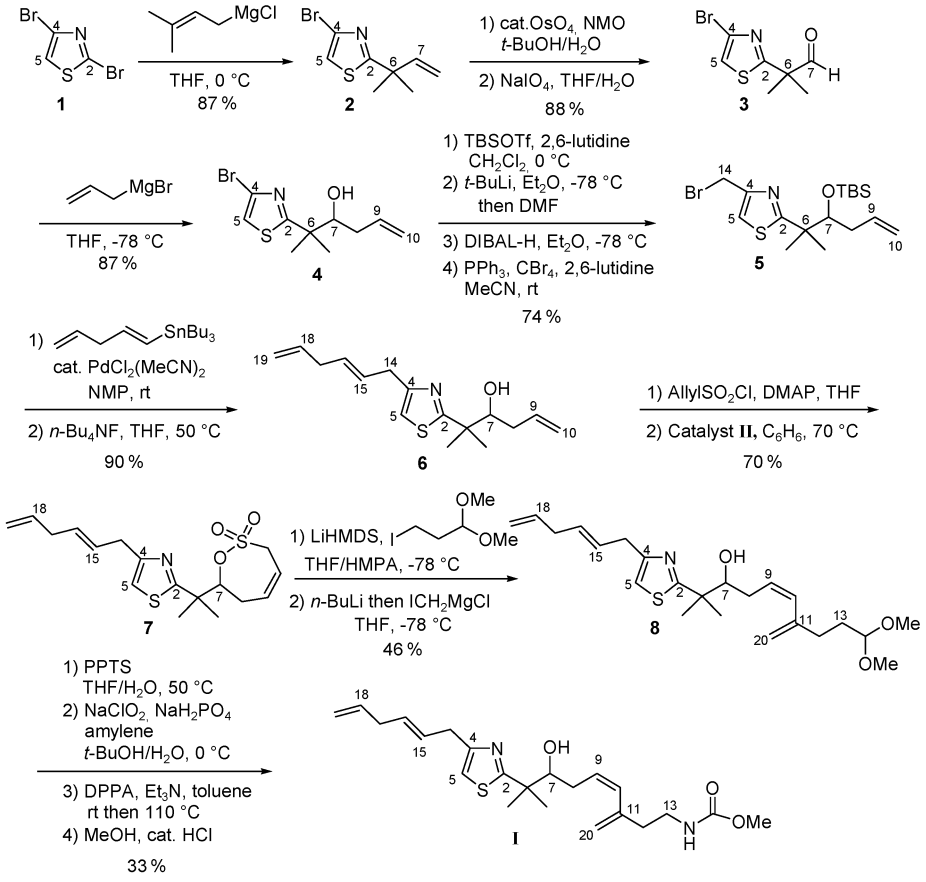
As this methodology allowed access to homoallylic conjugated (*Z*)-dienols from readily available homoallylic alcohols in four steps and with satisfactory overall yields [8], it has been included in our retrosynthetic analysis of the originally proposed structure of mycothiazole (compound **I**). The methyl carbamate moiety at C13 could be installed by a Schmidt reaction applied to the carboxylic acid of type **G** in which the elaboration of the conjugated (*Z*)-dienol moiety was envisaged from the corresponding homoallylic alcohol derivative of type **H** by using the previously described methodology. The introduction of the side chain at C4 in compound **H** should be achieved from the 2-substituted 4-bromothiazole **J** which, in turn, would be synthesized from the readily available 2,4-dibromothiazole **1** (Scheme 2).



Scheme 2

In order to introduce the side chain at C2 on the thiazole ring, 2,4-dibromothiazole **1** was treated with prenylmagnesium chloride, which reacts chemoselectively and with complete allylic transposition (S_E2' process) to produce the 2,4-disubstituted thiazole **2**. The terminal olefin in compound **2** was subjected to an oxidative cleavage to afford aldehyde **3** (OsO_4, NMO, then $NaIO_4$), and this latter compound was treated with allylmagnesium bromide to produce the secondary alcohol **4**. Compound **4** was transformed in four steps into the bromide **5** (protection as a *tert*-butyldimethylsilyl (TBS) ether, homologation at C4 by lithium–bromine exchange and formylation with dimethylformamide (DMF), reduction to the alcohol and bromination) which was then subjected to a Stille coupling with (*E*)-1-tributylstannylpenta-1,4-diene [$PdCl_2(MeCN)_2$, NMP, room temperature (rt)] to elaborate the nonconjugated dienic side chain at C4. After deprotection of the hydroxyl group at C7, the resulting homoallylic alcohol **6** was converted into the unsaturated sultone **7**, which subsequently produced the homoallylic conjugated (*Z*)-dienol **8** upon sequential alkylations, first with a functionalized alkyl iodide and then with ICH_2MgCl [8]. Four steps were then necessary to transform **9** into the originally proposed structure of mycothiazole **I**. After hydrolysis of the dimethyl acetal, the resulting aldehyde was oxidized to the corresponding carboxylic acid, which was converted into the acyl azide by treatment with diphenylphosphoryl azide (DPPA, Et_3N, toluene, rt). Subsequent thermolysis induced the Curtius rearrangement to the corresponding isocyanate whose methanolysis finally led to compound **I** (Scheme 3) [9,10].

The total (racemic) synthesis of the originally proposed structure of mycothiazole **I** was achieved in 18 steps from 2,4-dibromothiazole **1** with an overall yield of 5 %. It is worth noting that a formal enantioselective access to **I** was also demonstrated through the synthesis of the homoallylic alcohol **4** in high optical purity (ee = 99 %) by using an enantioselective allyltitanation [9,10].

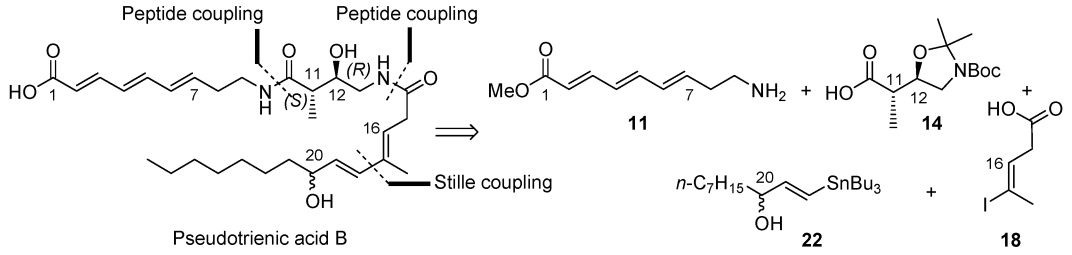


Scheme 3

PSEUDOTRIENIC ACID B

We were also interested in the synthesis of pseudotrienic acid B, a bioactive metabolite with antimicrobial activity, which has been recently isolated from *Pseudomonas* sp. 381-IODS [12]. Its structure was established by ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectroscopy and by electrospray ionization/mass spectrometry (ESI/MS). Pseudotrienic acid B was isolated as a 1/1 mixture of epimers at C20, but the absolute configurations at C11 and C12 are well defined as (*S*) and (*R*), respectively. Its molecular architecture is further characterized by a (*E*,*E*,*E*)-trienic conjugated acid (C1–C7), two amide bonds and a trisubstituted (*E*,*E*)-conjugated diene (C16–C19).

A highly convergent total synthesis of pseudotrienic acid B has been envisaged from four key fragments: the aminotrienoate **11**, the aminohydroxy acid **14**, the vinyl iodide **18**, and the vinyl stannane **22**. In order to assemble these four fragments, two peptide coupling reactions would be necessary to install the two amide bonds as well as a Stille coupling reaction to generate the trisubstituted (*E*,*E*)-diene (Scheme 4).



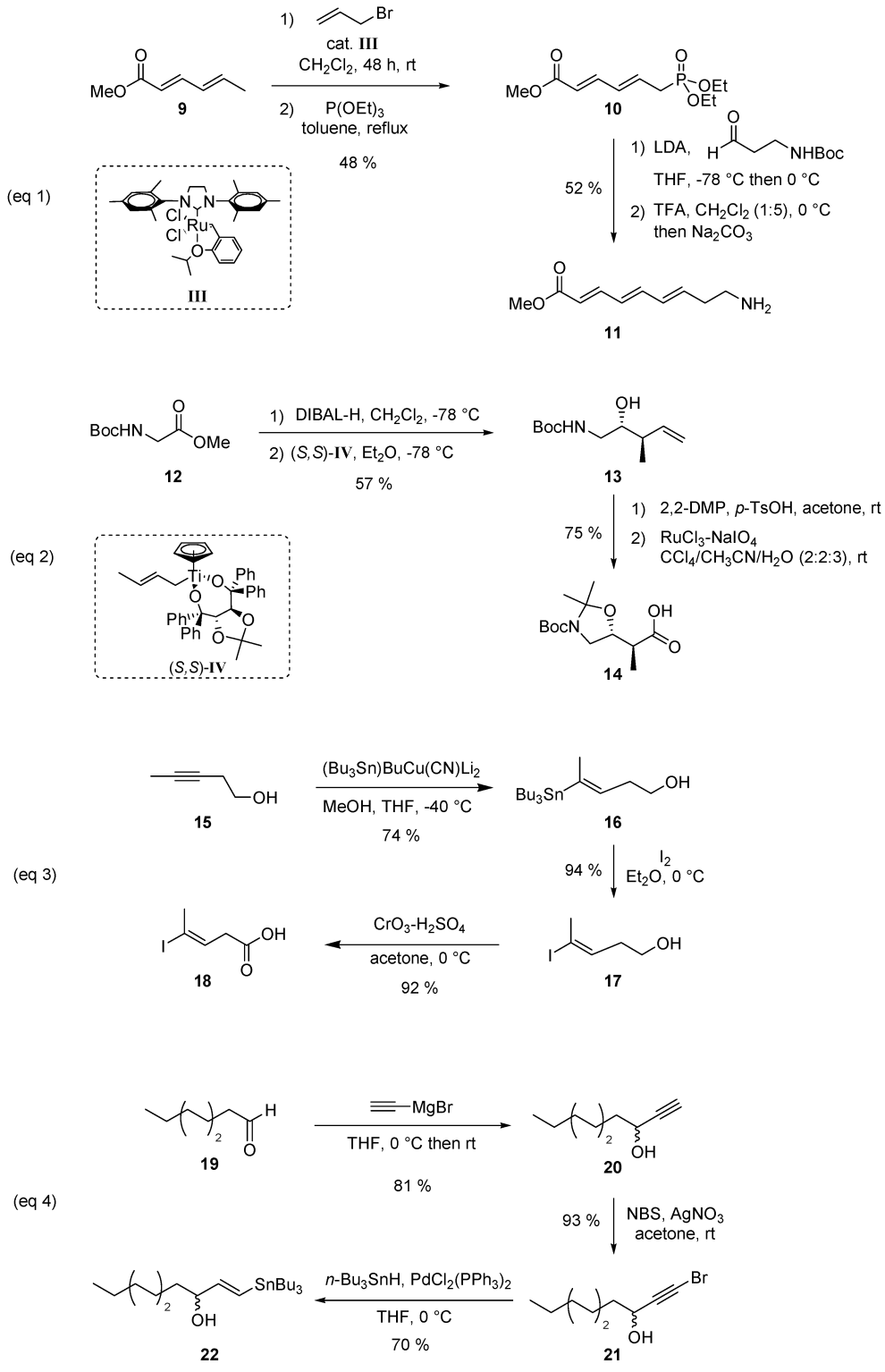
Scheme 4

In order to have a short and efficient synthesis of pseudotrienic acid B, the challenge was to obtain each of the four key fragments (**11**, **14**, **18**, and **22**) in three or four steps from commercially available starting materials. The synthesis of the aminotrienic ester **11** was achieved from methyl sorbate **9** and proceeded through cross-metathesis and a Horner–Wadsworth–Emmons (HWE) olefination as the key reactions. After treatment of methyl sorbate **9** with allyl bromide (5 equiv) in the presence of Grubbs–Hoveyda catalyst **III** (5 mol %) [13], the corresponding dienic allylic bromide was obtained with high stereoselectivity [(*E*,*E*)/(*E*,*Z*) > 95/5] and the latter was subsequently transformed into the corresponding diethylphosphonate **10** under Michaelis–Arbuzov conditions (48 % overall yield). A HWE olefination between phosphonate **10** and the *N*-Boc-protected 3-aminopropanal was then accomplished to produce, after trifluoroacetic acid (TFA)-mediated deprotection, the free trienic amino ester **11**. Thus, trienic ester **11** was synthesized efficiently in four steps from methyl sorbate **9** in 25 % overall yield (Scheme 5, eq. 1).

The amino acid **14**, which corresponds to the C10–C13 fragment of pseudotrienic acid B, was prepared from the commercially available *N*-Boc-protected glycine **12**. In order to control the configuration of the two stereogenic centers present at C11 and C12 in pseudotrienic acid B, the amino ester **12** was transformed into the corresponding aldehyde (diisobutylaluminum hydride, DIBAL-H) and directly treated with the highly face-selective crotyltitanium complex (*S*,*S*)-**IV** [14], which gave rise to the homoallylic amino alcohol **13** with high diastereo- and enantioselectivity (dr > 95/5; ee = 95 %) [15]. After protection of the resulting amino alcohol as the *N*,*O*-acetonide and oxidative cleavage of the terminal double bond under Sharpless conditions ($RuCl_3$–$NaIO_4$) [16], the desired carboxylic acid was isolated in 42 % overall yield (Scheme 5, eq. 2).

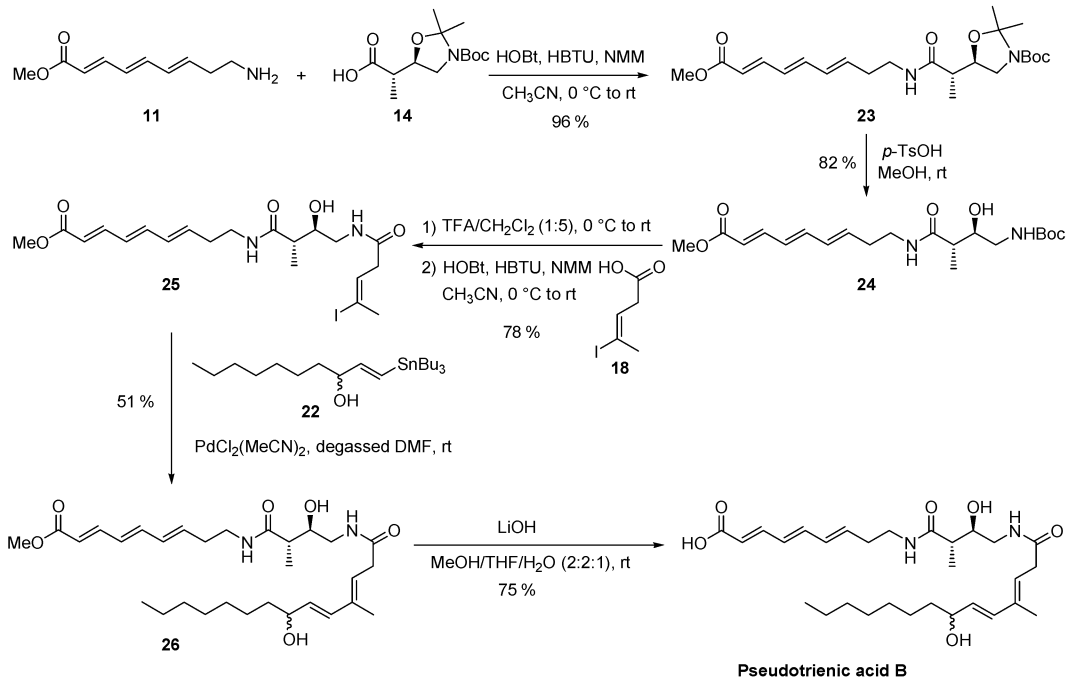
The synthesis of the required (*E*)-vinyl iodide **18**, which corresponds to the C14–C17 fragment, commenced from the commercially available pent-3-yn-1-ol **15**, which underwent a regio- and stereoselective stannylcupration by using the mixed higher-order cuprate [$(Bu_3Sn)BuCu(CN)Li_2$] [17], thus giving the vinyl stannane **20**. A subsequent iododestannylation of the latter compound followed by oxidation of the primary alcohol with Jones' reagent furnished the desired carboxylic acid **18** (64 % overall yield from pent-3-yn-1-ol **15**) (Scheme 5, eq. 3).

The last fragment, the vinyl stannane **21**, was prepared in three steps from octanal **19**, which was converted by a sequence of routine operations into the bromoalkyne **21**. Palladium-catalyzed regio- and stereoselective hydrostannylation of the latter compound using *n*-Bu_3SnH in the presence of $PdCl_2(PPh_3)_2$ afforded the desired alkenyl stannane **22** as a single stereoisomer. Thus, compound **22** was obtained in three steps from octanal with an overall yield of 53 % (Scheme 5, eq. 4).


1) Br
cat. III
CH_2Cl_2, 48 h, rt
2) $P(OEt)_3$
toluene, reflux
48 %
MeO
9
10
OEt
OEt
1) LDA, NHBoc
THF, -78 °C then 0 °C
52 %
2) TFA, CH_2Cl_2 (1:5), 0 °C
then Na_2CO_3
11
NH2
(eq 1)
III
Cl
Ru
N
O
BocHN
OMe
12
1) DIBAL-H, CH_2Cl_2, -78 °C
2) (S,S)-IV, Et_2O, -78 °C
57 %
OH
13
75 %
1) 2,2-DMP, p-TsOH, acetone, rt
2) $RuCl_3$-$NaIO_4$
$CCl_4/CH_3CN/H_2O$ (2:2:3), rt
14
BocN
(eq 2)
(S,S)-IV
Ti
Ph
15
$(Bu_3Sn)BuCu(CN)Li_2$
MeOH, THF, -40 °C
74 %
Bu_3Sn
16
94 %
I_2
Et_2O, 0 °C
17
(eq 3)
CrO_3-H_2SO_4
acetone, 0 °C
92 %
18
I
19
MgBr
THF, 0 °C then rt
81 %
20
93 %
NBS, $AgNO_3$
acetone, rt
21
Br
(eq 4)
n-Bu_3SnH, $PdCl_2(PPh_3)_2$
THF, 0 °C
70 %
22
$SnBu_3$

Scheme 5

With the four fragments in hands, the stage was set to probe the envisaged end game of the synthesis. At first, the carboxylic acid **14** was coupled with the aminotrienic ester **11** to afford amide **23** in 96 % yield. In order to build the C1–C17 fragment of pseudotrienic acid B, the *N*,*O*-acetonide and the *tert*-butyloxycarbonyl group in compound **23** were successively cleaved (*p*-TsOH, MeOH leading to **24** then TFA, CH_2Cl_2) and the obtained free aminoalcohol was subsequently coupled with the carboxylic acid **18** under classical peptide coupling conditions. The resulting vinyl iodide **25** was then involved in a Stille cross-coupling reaction with vinyl stannane **22**, catalyzed by $PdCl_2(MeCN)_2$, which successfully produced the core structure of pseudotrienic acid B, i.e., ester **26** (51 % yield). Finally, after a simple saponification of **26** with LiOH, the expected pseudotrienic acid B was isolated in 75 % yield. The spectroscopic data were in agreement with those reported in the literature for the natural product (Scheme 6). Thus, a concise, efficient, and highly convergent stereoselective synthesis of pseudotrienic acid B has been achieved with a longest linear sequence of 10 steps from methyl sorbate **9** with 5.8 % overall yield [18]. To our knowledge, this constitutes the first total synthesis of this naturally occurring molecule.



Scheme 6

By using very simple methodologies such as ring-closing metathesis and cross-metathesis reactions, efficient stereoselective syntheses of biologically active natural products as well as analogs can be achieved.

ACKNOWLEDGMENTS

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