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Natural Products

Asymmetric Total Synthesis of *ent*-Pyripyropene A

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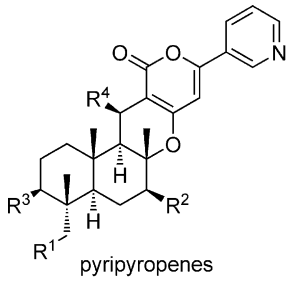
Abstract: An asymmetric total synthesis of *ent*-pyripyropene A was achieved by a convergent synthetic route. We used our originally developed Ti^{III}-catalyzed radical cyclization to construct an AB-ring portion that consisted of a *trans*-decalin skeleton with five contiguous stereogenic centers. The coupling between the AB-ring and the DE-ring portions, and a subsequent C-ring cyclization, led to the total synthesis of *ent*-pyripyropene A. An evaluation of the insecticidal activity of *ent*-pyripyropene A against two aphid species revealed that *ent*-pyripyropene A was 35–175 times less active than naturally occurring pyripyropene A. This result indicated that the biological target of pyripyropene A recognizes the absolute configuration of pyripyropene A.

Introduction

The isolation and structural determination of pyripyropenes A to D[1] and pyripyropenes E to L were reported by the Ōmura group more than two decades ago (Figure 1).[2] Pyripyropenes are mixed polyketide–terpenoids (meroterpenoids), and were isolated from *Aspergillus fumigatus*. Bioassay results have revealed that pyripyropenes A and C retain the highest degree of inhibitory activity against cholesterol acyltransferase (ACAT) among naturally occurring compounds.[1a,c] ACAT is regarded as a promising target for the development of anti-hypercholesterolemia agents.[3] Recently, molecular biological studies have revealed the presence of two isozymes, ACAT1 and ACAT2.[4] Selective ACAT2 inhibition is thought to be preferable for the development of anti-atherosclerotic agents, whereas ACAT1 inhibition might cause detrimental effects.[5] From this point of view, pyripyropene A and its synthetic analogues are attractive because pyripyropene A is known to exert highly selective inhibitory activity against ACAT2.[6]



pyripyropenes

A: $R^1 = R^2 = R^3 = OAc$, $R^4 = OH$
B: $R^1 = OCOEt$, $R^2 = R^3 = OAc$, $R^4 = OH$
C: $R^1 = OAc$, $R^2 = OCOEt$, $R^3 = OAc$, $R^4 = OH$
D: $R^1 = R^2 = OAc$, $R^3 = OCOEt$, $R^4 = OH$
E: $R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = H$
F: $R^1 = R^2 = H$, $R^3 = OCOEt$, $R^4 = H$
G: $R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = OH$
H: $R^1 = R^2 = H$, $R^3 = OCOEt$, $R^4 = OH$
I: $R^1 = R^2 = R^3 = OCOEt$, $R^4 = OH$
J: $R^1 = OAc$, $R^2 = R^3 = OCOEt$, $R^4 = OH$
K: $R^1 = R^3 = OCOEt$, $R^2 = OAc$, $R^4 = OH$
L: $R^1 = R^2 = OCOEt$, $R^3 = OAc$, $R^4 = OH$

Figure 1. Chemical structures of pyripyropenes A to L.

In 1995, the Gloer group isolated pyripyropene A from *Eupenicillium reticulisporum*, and first reported the insecticidal activity of pyripyropene A against the corn earworm.[7] Ten years later, Kim et al. assumed that ACAT inhibitors would be good

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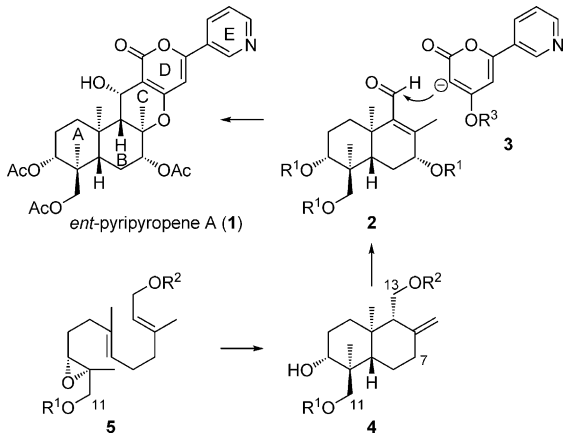
insecticidal agents because insects essentially require sterols for their growth and utilize a sterol-acylating enzyme that participates in the storage and transport of sterols and in the activation and degradation of hormones. Kim et al. actually confirmed that ACAT inhibitors, which included pyripyropene A, exert insecticidal activity against both the corn earworm and the mealworm.[8] Moreover, Goto et al. recently reported that pyripyropenes also retain potent insecticidal activity against aphids.[9]

The Ōmura–Smith group achieved the first total synthesis of pyripyropene A in a highly convergent manner.[10] However, their total synthesis included several steps that cannot be scaled up.[11] Therefore, the Ōmura–Nagamitsu group developed a practical, linear synthetic route for the total synthesis of pyripyropene A.[11] They successfully synthesized pyripyropene analogues with a simplified A-ring structure based on their developed synthetic route.[12] Herein, we wish to report the convergent synthesis of *ent*-pyripyropene A based on our originally developed tandem radical cyclization by using a catalytic amount of a Ti^{III} reagent.[13]

We were interested in the insecticidal activity of *ent*-pyripyropene A (**1**) that has not yet been reported, although numerous analogues of naturally occurring pyripyropene A have been synthesized and their biological activities have been evaluated (Scheme 1).[6b,d–f,14] We planned to develop a convergent synthetic route that would enable ready access to various pyripyropene analogues in the future. Our synthetic plan is shown in Scheme 1. The nucleophilic addition of DE-ring carbanion **3** to the AB-ring aldehyde **2**, oxidation of the generated allylic alcohol to the corresponding enone, stereoselective construction of a C-ring by oxa-Michael addition, and the following stereoselective reduction[10a] of a ketone would lead to pyripyropene A (**1**). The AB-ring **2** would be synthesized from **4** by the introduction of a hydroxy group at the 7-position, isomerization of an alkene, and oxidation of the 13-OH group. The *trans*-decalin **4** containing five contiguous stereogenic centers would be constructed by tandem radical cyclization of the enantiomerically pure epoxy alkene **5** by using a catalytic amount of a Ti^{III} reagent. This synthetic plan would allow the synthesis of either the natural compound or its enantiomer because both enantiomers of epoxy alkene **5** can be readily prepared by Sharpless–Katsuki asymmetric epoxidation of the corresponding allylic alcohol.[15]

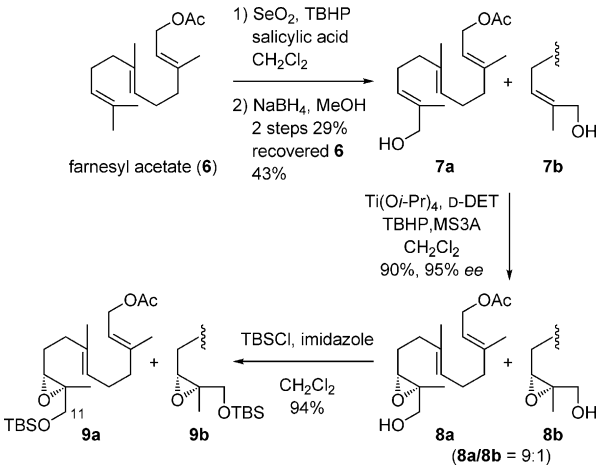


Scheme 1. Synthetic plan for *ent*-pyripyropene A (**1**).

A key to the total synthesis was the construction of *trans*-decalin **4** by tandem radical cyclization. Pioneering work for the construction of the 11-desoxo congener of *trans*-decalin **4** from farnesyl acetate by tandem radical cyclization was reported by the Breslow group more than 45 years ago.[16] In 2001, the Barrero group demonstrated the synthesis of the 11-desoxo congener of **4** from an epoxy alkene[17] by tandem radical cyclization using a stoichiometric amount of a Ti^{III} reagent under conditions that were originally reported by Nugent and Rajanbabu.[18] At the same time, we also reported the synthesis of a 13-desoxo-congener of **4** that was used for the synthesis of smenospondiol by using a stoichiometric amount of a Ti^{III} reagent.[19] In 2006, the Barrero group reported the radical cyclization of **5** ((R^1 = *tert*-butyldimethylsilyl (TBS), R^2 = acetyl (Ac)) in the presence of a catalytic amount of Ti^{III} using trimethylsilyl chloride (TMSCl)/2,4,6-collidine additives[20] to afford **4** (R^1 = TBS, R^2 = Ac) in a moderate yield (41%).[21] However, Oikawa et al. reported that they performed the cyclization of **5** (R^1 = TBS, R^2 = Ac) by using a stoichiometric amount of a Ti^{III} reagent (41% yield) because Barrero's catalytic conditions were not suitable for providing the desired product.[22] Since we independently reported radical cyclization conditions using a catalytic amount of a Ti^{III} reagent with BEt_3/TMSCl or BEt_3/2,6-lutidine·HCl additives,[13] we planned to apply the above conditions to the asymmetric synthesis of AB-ring **4**.[23]

Results and Discussion

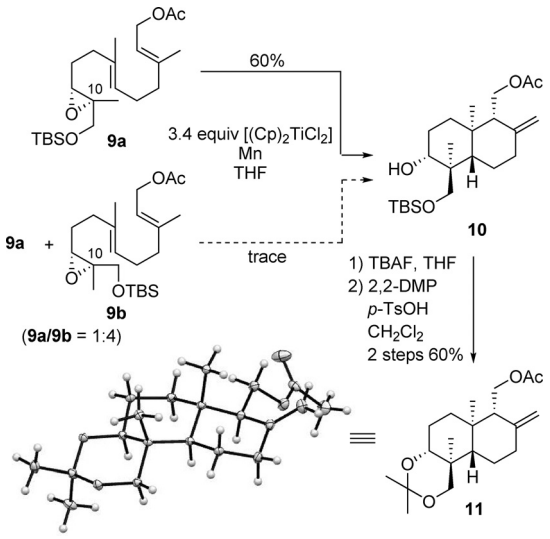
Cyclization precursor **9** was prepared from farnesyl acetate (**6**) in four steps, as shown in Scheme 2. Allylic oxidation of **6** afforded alcohol **7** as a 9:1 mixture of *E*/*Z*-isomers **7a** and **7b**,[24] which could not be separated by column chromatography. Therefore, the Sharpless–Katsuki asymmetric epoxidation[15] of



Scheme 2. Preparation of cyclization precursor **9**. TBHP = *tert*-butyl hydroperoxide, DET = diethyl tartrate, MS = molecular sieve.

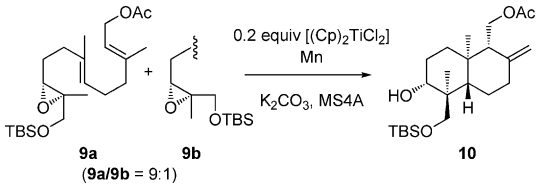
the mixture of the allylic alcohols **7a** and **7b** was carried out. The mixture of epoxy alcohols **8a** and **8b** was obtained in a high yield and in good enantiomeric excess (*ee*). The major isomer **8a** was isolated by careful silica-gel column chromatography. However, minor isomer **8b** could not be purely isolated and a 1:4 mixture of **8a** and **8b** was obtained. Thus, we assigned all the ^{1}H NMR spectroscopic signals for both **8a** and **8b**. From ^{1}H NMR spectroscopic analysis of the crude product of this epoxidation, we determined that the ratio of **8a** and **8b** was 9:1. The *ee* was determined by chiral HPLC analysis after converting the isolated epoxy alcohol **8a** to the corresponding benzoate (for details for determination of the *ee*, see the Supporting Information). We conducted a preliminary examination of the protecting groups (TBS, 4-methoxyphenyl methyl (MPM), methoxymethyl (MOM), Ac, and benzoyl (Bz)) for R^1 of **5** in a key radical cyclization, and the TBS protection afforded the best results. This observation was consistent with our previous results in the synthesis of smenospondiol.[19a] Therefore, the cyclization of precursor **9** with a TBS group was prepared, as shown in Scheme 2.

The influence of the stereochemistry at the 10-position on radical cyclization was examined by using pure **9a**, and a mixture of **9a** and **9b** (**9a**/**9b** = 1:4), as shown in Scheme 3. As a result, cyclization of the pure **9a** afforded the desired cyclization product **10** in a 60% yield. Surprisingly, the cyclization of the mixture of **9a** and **9b** afforded a complex mixture that contained only a trace amount of the desired cyclization product **10**. This result indicates that the isomer **9a** is a suitable cyclization precursor, while isomer **9b** is not. The relative stereochemistries of the cyclization products were unambiguously determined by X-ray crystallographic analysis of **11** that was derived from **10**.[25]



Scheme 3. Tandem radical cyclization of epoxy alkenes **9a** and **9b** mediated by stoichiometric amounts of Ti^{III} reagent, and determination of the stereochemistries of the cyclization product by X-ray crystallographic analysis of **11**. TBAF = tetrabutylammonium fluoride, 2,2-DMP = 2,2-dimethoxypropane.

Table 1. Examination of Ti^{III}-catalyzed tandem radical cyclization conditions.

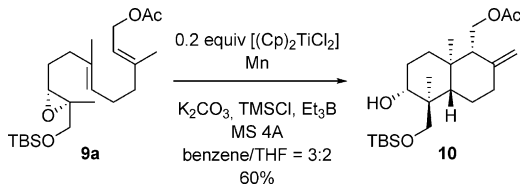


Entry	T [°C]	Additive	Solvent	Yield [%][a]
1	RT	Et_3B/TMSCl	THF	15
2	−20 to RT	Et_3B/TMSCl	THF	43
3	−20 to RT	Et_3B/TMSCl	toluene/THF = 3:2	44
4	−20 to RT	Et_3B/TMSCl	benzene/THF = 3:2	51
5	RT	Et_3B/2,6-lutidine·HCl	THF	45
6	60	Et_3B/2,6-lutidine·HCl	THF	46
7	60	Et_3B/2,6-lutidine·HCl	benzene/THF = 3:2	46

[a] Isolated yield.

The catalytic conditions were examined using a readily available mixture of **9a** and **9b** (**9a**/**9b** = 9:1), as shown in Table 1. In accordance with our previously developed procedure,[13] the additives Et_3B/TMSCl (entries 1–4) and Et_3B/2,6-lutidine·HCl (Table 1, entries 5–7) were examined. The combinations of Et_3B/TMSCl at room temperature resulted in a low yield (entry 1), which was probably due to an undesired generation of chlorohydrin. To suppress the undesired chlorohydrin formation, the reaction was carried out at a lower temperature (entry 2). As expected, the yield of **10** was improved. Solvent effects were examined as shown in entries 2–4. As a result, the use of a mixed solvent (benzene/THF = 3:2) afforded the best yield (51% in entry 4). Alternative additives, Et_3B/2,6-lutidine·HCl, provided the desired product (entries 5–7), but the yields were up to 46%.

The tandem radical cyclization of the isolated epoxy alkene **9a** was carried out by using the optimized catalytic conditions (Table 1, entry 4), as shown in Scheme 4. The manganese powder, K_2CO_3, MS4A, and a solution of **9a** (1.0 equiv) in benzene, all were placed in a round-bottomed flask. After stirring at room temperature for 1 h, the mixture was frozen by cooling at −20 °C. To the frozen mixture, a supernatant of $[(Cp)_2TiCl]$ (Cp = cyclopentadienyl; 0.20 equiv) in THF that was prepared in situ by mixing $[(Cp)_2TiCl_2]$ and Mn, was added dropwise at −20 °C. Then, solutions of TMSCl in benzene and Et_3B in THF were added successively at −20 °C. After stirring at room temperature, the standard workup procedure and silica-

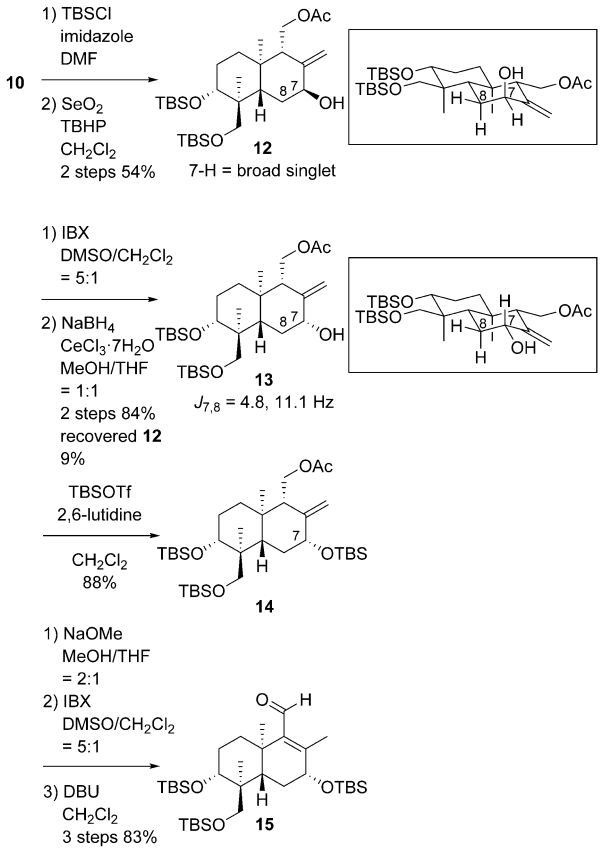


Scheme 4. Ti^{III}-catalyzed tandem radical cyclization of the isolated epoxy alkene **9a**.

gel column chromatographic separation afforded the desired product **10** in a 60% yield.

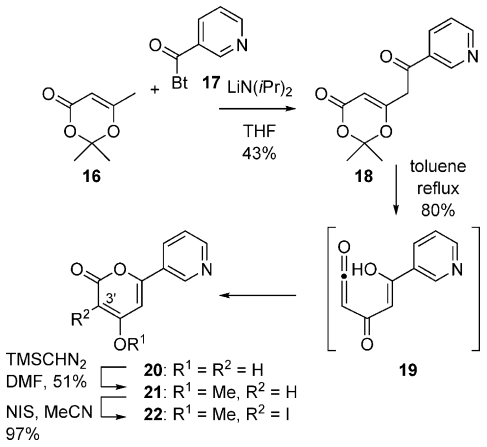
The automation of synthetic procedures improves both the reproducibility and the reliability of the syntheses because automated synthesizers minimize the variability of the experimental manipulations.[26] We carried out the synthesis of **10** including the key step, Ti^{III}-catalyzed radical cyclization by using our originally developed automated synthesizer, ChemKonzert[26c] (for details of the automated synthesis of **10**, see the Supporting Information). This automation is noteworthy because the obtained compound **10** is useful for the synthesis of numerous bioactive natural products.

The cyclization product **10** was converted to AB-ring **15**, as shown in Scheme 5. After the protection of the secondary alcohol with a TBS group, the hydroxy group was introduced at the 7-position to afford allylic alcohol **12**. The stereochemistry of the 7β-OH group in **12** was determined by ^{1}H NMR spectroscopic analysis (7α-H was observed as a broad singlet). The stereochemistry of the 7β-OH group in **12** was inverted by the oxidation–reduction sequence. In the Luche reduction,[27] the hydride attacked from the sterically less-hindered β-face to afford the desired 7α-alcohol **13** as a major product (7α-OH/7β-OH = 84%:9%). The stereochemistry of the 7α-OH in **13** was confirmed by ^{1}H NMR spectroscopic analysis ($J_{7,8}$ = 4.8, 11.1 Hz). The following protection of the alcohol with a TBS group afforded **14**. After removal of the acetyl group, the resultant alcohol was oxidized to the corresponding aldehyde. A subsequent isomerization of the alkene in the presence of DBU afforded the desired enal **15**[28] in a good yield.



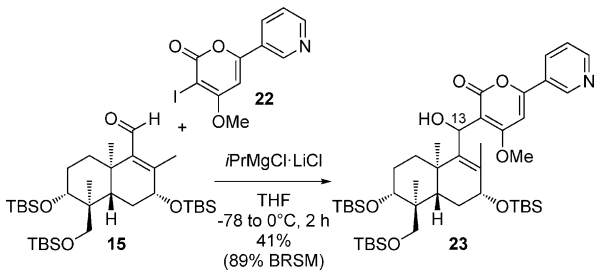
Scheme 5. Synthesis of AB-ring **15**. IBX = 2-iodoxybenzoic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

The DE-ring portion was prepared in accordance with the previously reported Katritzky synthesis of 6-phenyl-4-hydroxy-2-pyrone, as shown in Scheme 6.[29] Thus nucleophilic acyl substitution of **17** with the carbanion generated from 2,2,6-trimethyl-1,3-dioxin-4-one (**16**) provided **18**.[30] The acyl ketene **19** was in situ generated by a retro-Diels–Alder reaction of **18** under heating, and the subsequent spontaneous cyclization afforded the desired pyridyl pyrone **20** in a good yield. We prepared methylated- and iodinated-pyridylpyrones **21** and **22** as candidates for the DE-ring portion as the coupling partner of AB-ring **15**.



Scheme 6. Preparation of DE-rings **20**–**22**. NIS = *N*-iodosuccinimide.

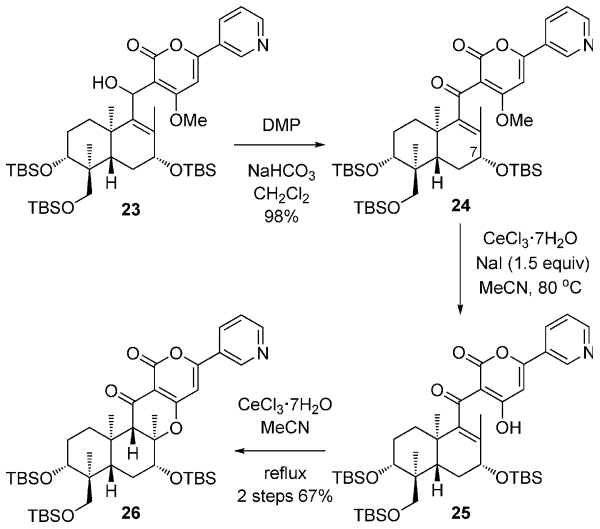
Unfortunately, extensive attempts failed to generate the desired anions at the 3′-position in DE-rings **20** and **21** with *t*BuLi. In the case of **20**, an undesired addition of *t*BuLi to the pyridine ring occurred.[31] It was difficult to suppress this undesired addition by controlling either the temperature or the quantity of *t*BuLi. In the case of **21**, an undesired nucleophilic acyl substitution to the pyrone ring occurred and the pyrone ring was cleaved. These results turned our attention to generating the desired anion from alkenyl iodide **22** with a Grignard reagent, as shown in Scheme 7.[32] A THF solution of *i*PrMgCl·LiCl[33] was added at −78 °C to a suspension of **22** in THF, and the reaction mixture was stirred at the same temperature for



Scheme 7. Coupling between AB-ring **15** and DE-ring **22**.

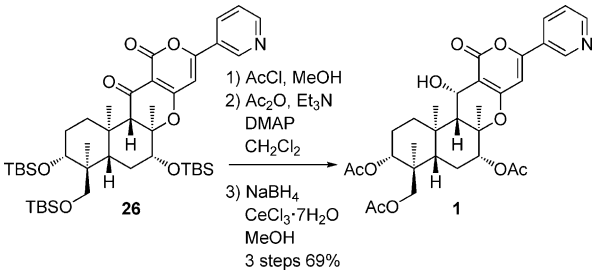
20 min under an Ar atmosphere. A solution of aldehyde **15** in THF was added dropwise to the reaction mixture at the same temperature. After stirring at 0 °C for 2 h, a standard workup procedure afforded the desired coupling product **23** in a 41% yield with a 54% recovery of enal **15** (89% yield BRSM). Although the stereochemistry of the 13-OH was not determined, a single stereoisomer was obtained in this coupling reaction. It should be noted that approximately 30% of DE-ring that was used was also recovered as the desiodo compound **21**. This recovered **21** was reusable for the coupling reaction after iodination to **22**. Although the yield of the key coupling reaction was moderate, this reaction was rather clean. Only three compounds, unreacted **15**, desiodo compound **21**, and the desired product **23** were observed in the crude reaction mixture. These compounds could be readily separated by silica-gel column chromatography.

The obtained alcohol **23** was oxidized in the presence of Dess–Martin periodinane (DMP)[34] to the corresponding ketone **24** (Scheme 8). The following removal of the methyl



Scheme 8. C-ring cyclization for the synthesis of **26**.

group was carried out in accordance with the conditions established by Yadav using $CeCl_3 \cdot 7H_2O$ and NaI.[35] In this reaction, both the temperature and the quantity of the reagents were important for a good yield. Either a higher temperature or the use of a larger amount of reagents caused the undesired elimination of the TBSO group at the 7-position. An attempt for a one-pot operation to obtain the cyclized product **26** from **24** resulted in the undesired elimination of the TBSO group. Because heating conditions (MeCN, reflux) were necessary for the desired C-ring cyclization, however, in the presence of NaI, these heating conditions caused the undesired elimination of the TBSO group. For these reasons, after the removal of the methyl group, the obtained enol **25** was roughly purified by short-pass column chromatography. $CeCl_3$-mediated cyclization then was performed to afford the desired product **26**[28] in a good yield (2 steps, 67%). The undesired elimination of the



Scheme 9. Completion of the total synthesis of *ent*-pyripyropene A (**1**). DMAP = 4-(dimethylamino)pyridine.

TBSO group did not proceed in the absence of NaI even at the reflux temperature.

In accordance with the procedure reported by the Ōmura–Nagamitsu group,[11] **26** was converted to *ent*-pyripyropene A (**1**) as shown in Scheme 9. Three TBS groups were removed by in situ generated HCl, and the acetyl groups then were introduced. The final Luche reduction[27] afforded the desired **1** in a good yield. The structure of **1** was confirmed by ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra, as well as by specific rotation. The observed spectra were consistent with the previously reported data except for the opposite sign of its specific rotation.[10a,11]

The insecticidal activity of both *ent*-pyripyropene A (**1**) and naturally occurring pyripyropene A was tested against two aphid species (*Megoura viciae* and *Myzus persicae*), as shown in Table 2 (for details of the evaluation of insecticidal activity, see

Table 2. Evaluation of insecticidal activity of *ent*-pyripyropene A and naturally occurring pyripyropene A against two aphid species.

Entry	Compound	Aphid	ED_{50} [ppm]
1	*ent*-pyripyropene A	*Megoura viciae*	666
2	*ent*-pyripyropene A	*Myzus persicae*	273
3	pyripyropene A	*Megoura viciae*	4
4	pyripyropene A	*Myzus persicae*	8

the Supporting Information). It was interesting that *ent*-pyripyropene A (**1**) retained a much weaker degree of insecticidal activity against both aphid species compared with pyripyropene A. The observed ED_{50} values were 35–175 times higher than those of pyripyropene A. This result indicates that the biological target of pyripyropene A recognizes the absolute configuration of pyripyropene A, because the enantiomeric pairs of pyripyropene A had almost identical physical properties. This is noteworthy because *ent*-pyripyropene A can be used as an ideal negative control for the detection of the biological target[36] of pyripyropene A in the future.

Conclusion

We achieved the asymmetric total synthesis of unnatural *ent*-pyripyropene A (**1**). Our originally developed Ti^{III}-catalyzed radical cyclization conditions using Et_3B/TMSCl were successfully

applied to the rapid construction of **10**, which consisted of a *trans*-decalin skeleton with five contiguous stereogenic centers. The coupling between the functionalized AB-ring **15** and DE-ring **22** was successfully performed by a Grignard addition reaction. A subsequent C-ring cyclization that was mediated by $CeCl_3$ led to the first total synthesis of *ent*-pyripyropene A (**1**). An evaluation of insecticidal activity revealed that the *ent*-pyripyropene A (**1**) was 35–175 times less active than naturally occurring pyripyropene A. This result indicates that the biological target of pyripyropene A recognizes the absolute configuration of pyripyropene A.

Experimental Section

Experimental details are given in the Supporting Information.

Acknowledgements

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Keywords: insecticidal activity · meroterpenoids · natural products · radical reactions · titanium

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