Tetrahedron Letters 51 (2010) 4425–4428

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Stereoselective construction of quaternary chiral centers using Ti(III)-mediated opening of 2,3-epoxy alcohols: studies directed toward the synthesis of penifulvins ☆

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ARTICLE INFO

*Article history:*
Received 21 May 2010
Revised 14 June 2010
Accepted 15 June 2010
Available online 18 June 2010

*Keywords:*
Penifulvin
Ti(III)-mediated epoxide opening
Radical cyclization
Quaternary chiral center

ABSTRACT

A trisubstituted α,β-unsaturated ester moiety was suitably placed in a molecule also bearing an epoxy alcohol moiety at its other end to intramolecularly trap the intermediate radical, which was formed when the molecule was treated with $Cp_2Ti(III)Cl$ to regio- and stereoselectively open its epoxy ring, giving rise to a quaternary chiral center. The method was subsequently used in an attempt to construct the bicyclic core framework of potent insecticides penifulvins.

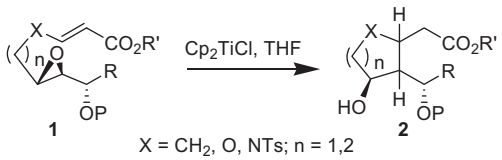


In our previous studies, we have shown that Ti(III)-mediated opening of chiral 2,3-epoxy alcohols[1] followed by intramolecular trapping of the resultant intermediate radicals by a suitably placed electron-deficient double bond leads to the formation of highly functionalized carbocycles,[2] oxacycles,[3] and azacycles[4] as shown in Scheme 1.

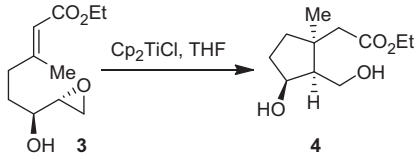
In the present Letter, we extend our work further to the synthesis of substituted ring systems, shown in Scheme 2, by using trisubstituted double bond in epoxy alcohol **3** to trap the intermediate radical, generated on treatment with $Cp_2Ti(III)Cl$, giving rise to stereoselective construction of quaternary chiral center in the carbocyclic ring of **4**. The method developed herein was subsequently applied in our ongoing studies directed toward the syntheses of novel antiinsectan sesquiterpenoid penifulvins A–E.[5,6]

Synthesis of **3** started with the mono protection of 1,4-butane diol **5** (Scheme 3). Oxidation and vinyl Grignard addition furnished the allylic alcohol **6** which after a protection–deprotection sequence gave the alcohol **7**. Carbinol **8** was obtained from compound **7** in two steps.

Oxidation and subsequent Horner–Wadsworth–Emmons olefination[7] of the resulting methyl ketone gave the *E*-olefin **9** as a major product. Deprotection of **9** was followed by Sharpless kinetic resolution[8] to provide the chiral epoxy alcohol **3** (ee >92%). Now with epoxy alcohol **3** in hand, the stage was set to implement the crucial Ti(III)-mediated epoxide opening followed by cyclization. Indeed, on exposure to the $Cp_2Ti(III)Cl$ reagent, generated in situ from $Cp_2TiCl_2$ and Zn dust and freshly fused $ZnCl_2$,[9] compound **3** underwent epoxide opening at 'C2 position' from the hydroxy side[1] and gave rise to a radical intermediate that was




**Scheme 1.** Stereoselective syntheses of highly substituted carbo-, oxa-, and azacycles using Ti(III)-mediated opening of 2,3-epoxy alcohols.




**Scheme 2.** Stereoselective synthesis of highly substituted cyclopentane ring system with a quaternary chiral center using Ti(III)-mediated opening of 2,3-epoxy alcohol.

☆ CDRI Communication No. 7940.

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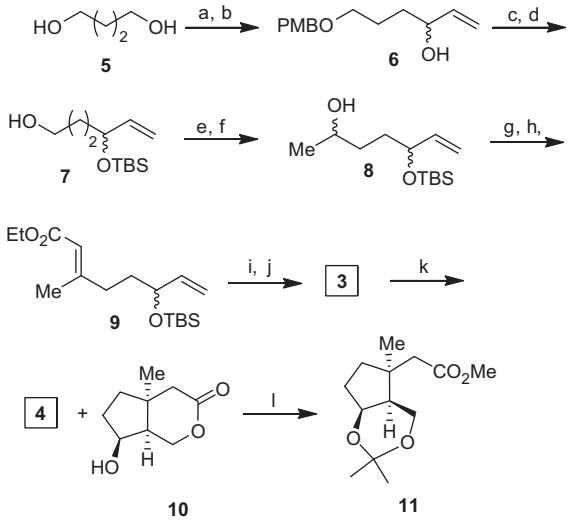
doi:10.1016/j.tetlet.2010.06.076




**Scheme 3.** Synthesis of **4**; Reagents and conditions: (a) NaH, PMBBr, TBAI, THF, 0 °C to rt, 12 h, 60%; (b) (i) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 to 0 °C, 1 h, (ii) vinylmagnesium bromide, THF, 0 °C, 15 min, 75% yield in two steps; (c) TBDMSCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C to rt, 12 h, 95%; (d) DDQ, $CHCl_3$:buffer (pH 7): 20:1, rt, 1 h, 85%; (e) $SO_3$-Py, $Et_3N$, $CH_2Cl_2$–DMSO (1:1.6), 0 °C, 30 min; (f) $CH_3MgI$, $Et_2O$, 0 °C, 10 min, 75% yield in two steps; (g) Dess–Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 9 h, 88%; (h) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C to rt, 24 h, 75%; (i) TBAF, THF, 0 °C, 3 h, 78%; (j) $Ti(O^iPr)_4$, L(+)-DIPT, TBHP, MS (4 Å), $CH_2Cl_2$, −20 °C, 48 h, 35%; (k) $Cp_2TiCl_2$, Zn, $ZnCl_2$, THF, −20 °C to rt, 18 h, 65% (based on recovered starting material); (l) 2,2-dimethoxypropane, $CH_2Cl_2$, CSA, rt, 24 h, 85%.

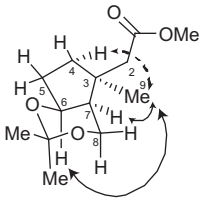
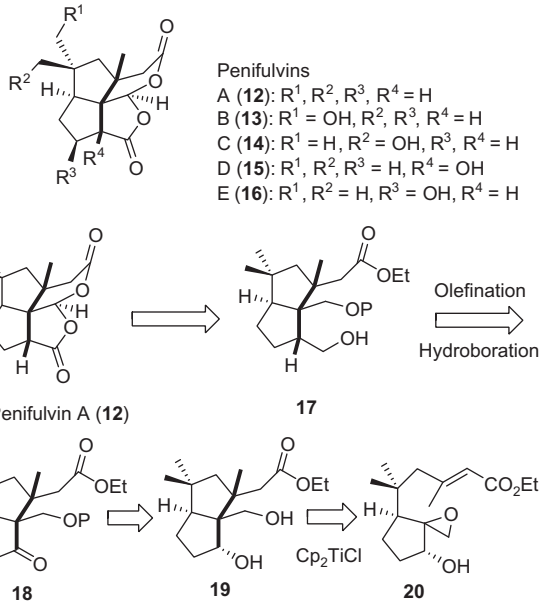



**Figure 1.** Important NOEs that were used to establish the relative stereo positions of H6, H7, and Me(9) of **11**.

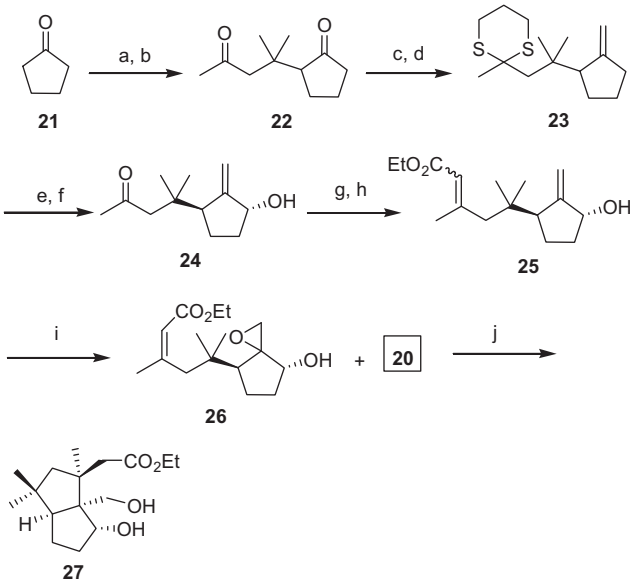
intramolecularly trapped by the trisubstituted α,β-unsaturated ester moiety leading to the formation of the substituted cyclopentane ring **4** as the major product along with the six-membered lactone **10** in about 65% yield (based on 15% recovered starting material). Small amounts of some unidentified products, less polar than the starting material, were also formed. The inseparable mixture of **4** and **10** (1:1) was treated with 2,2-dimethoxypropane under acid-catalyzed conditions to give a single product **11** in 85% yield.[10]

The stereochemistry of **11** was determined by using the $^1H$ and 2D NOESY experiments. Some of the important NOEs are shown in Figure 1. $^3J_{6-7}$ of about ∼5 Hz and NOEs between H6–H4(down) and H7–H4(down) suggest that H6 and H7 protons are having a dihedral angle of ∼30°, which are in axial, equatorial disposition at C6 and C7 of the six-membered skewed chair conformation. Also, NOEs between H7–Me(9), H6–Me(9), and H4(down)–Me(9) suggest that H7 and Me(9) are cis fused.

To demonstrate the practical applicability of the method, it was applied in our ongoing studies directed toward the synthesis of penifulvins. Penifulvins A–E (**12**–**16**, Scheme 4) were isolated from an organic extract of cultures of *Penicillium griseofulvum* NRRL35584 and showed potent antifungal and antiinsectan activities in preliminary assays against the fall armywarm.[5,6] The overall structure of penifulvins has dioxa[5.5.5.6]fenestrance ring system




**Scheme 4.** Structures of penifulvins and retrosynthetic analysis of penifulvin A (**12**).




**Scheme 5.** Synthesis of **27**; Reagents and conditions: (a) LDA, TMSCl, THF, 0 °C, 2 h; (b) mesityl oxide, $TiCl_4$, $CH_2Cl_2$, −78 °C, 1 h, 56% (in two-steps); (c) $CH_2(CH_2–S–TMS)_2$, $ZnI_2$, ether, rt, 10 h, 54%; (d) Mg, $TiCl_4$, THF, $CH_2Cl_2$, 0 °C, 2 h, 62%; (e) $SeO_2$, TBHP, $^tBuOH$, 50 °C, 12 h, 39%; (f) $AgNO_3$, EtOH–$H_2O$, 50 °C, 30 min, 90%; (g) ethyl ethynyl ether, *n*-BuLi, THF, −78 °C, 4 h, 72%; (h) $AuCl_3$, $CH_2Cl_2$–EtOH, rt, 15 min, 91%; (i) *m*-CPBA, $CH_2Cl_2$, 0 °C, 2 h, 85%; (j) $Cp_2TiCl_2$, Zn, $ZnCl_2$, THF, rt, 14 h, 82%.

in which four rings share a central quaternary carbon. Additionally there are two (except penifulvin D, having three) more quaternary carbons, a γ- and δ-lactone sharing the acylal center and a total of five (except penifulvin E, having six) stereo centers congested on a 15 carbon skeleton. The biological activities and challenging structures of penifulvins have attracted the attention of synthetic chemists.[11]

Due to the very few methods available for the construction of functionalized quaternary centers[12] and the presence of several such centers in penifulvins, we felt that the method we have in

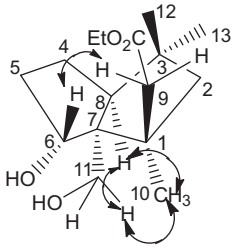



**Figure 2.** Important NOEs that were used to establish the relative stereochemistries in **27**.

hand to build chiral quaternary centers using Ti(III)-mediated ring opening of 2,3-epoxy alcohols could be tested for its practical applicability in assembling the core bicylic ring system of these molecules.

Retrosynthetic analysis of one of the penifulvins, penifulvin A (**12**) is illustrated in Scheme 4. We envisaged that compound **12** could have been derived from intermediates **17–19** via functional groups manipulations. The bicylic core of **19** could be obtained from epoxy alcohol **20** via $Cp_2TiCl$-mediated radical cyclization.

We commenced our synthesis from commercially available starting material cyclopentanone **21** as shown in Scheme 5. The first step involved a crucial Michael addition reaction[13] in which cyclopentanone **21** was first converted to the corresponding TMS enol ether derivative using LDA and TMSCl in THF at −78 °C. The TMS-enol ether intermediate, without purification and characterization, was mixed with mesityl oxide in $CH_2Cl_2$ and the mixture was added dropwise to a $TiCl_4$ solution in $CH_2Cl_2$ at −78 °C to give **22** in 56% yield. Next our objective was to protect selectively one of the carbonyl groups of **22**. We achieved it by treating **22** with 1,3-propanedithiobis(trimethylsilane) and $ZnI_2$ in diethyl ether at room temperature.[14] A variety of reagents and conditions, such as $(CH_2OH)_2$, PTSA, benzene; $CH_2(CH_2OH)_2$, PTSA, benzene; $(CH_2OTMS)_2$, TMSOTf, $CH_2Cl_2$; $CH_2(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, and $CH_2Cl_2$ were used but none of them were found to be effective except the above-mentioned condition.

The resulting mono-keto compound was then subjected to one carbon olefination. Several reagents and conditions such as $Ph_3P^+CH_3I^-$, *n*-BuLi, THF; $Ph_3P^+CH_3I^-$, KO$^t$Bu, diethyl ether; $Cp_2TiMe_2$, and toluene were used but none of them gave the desired product. Finally the transformation was successfully carried out using Mg and $TiCl_4$ in $CH_2Cl_2$–THF solvent mixture at 0 °C to afford **23** in 62% yield.[15] Allylic oxidation of **23** using $SeO_2$ and TBHP in $^t$BuOH at 50 °C gave the desired allylic alcohol in 39% yield.[16] Extensive decomposition of the starting material was observed when other reagents and conditions such as $SeO_2$, $H_2O_2$, dioxane; $SeO_2$, $H_2O_2$, $^t$BuOH; and $SeO_2$, AcOH–$H_2O$ were used. The relative stereochemistry of the newly generated center carrying the –OH group was established latter by NOESY spectroscopy. Next, to deprotect the dithiane moiety, the allylic alcohol intermediate was treated with $AgNO_3$ in EtOH at 50 °C to give **24** in 90% yield.[17]

Our next objective was to carry out two carbon olefination reaction. A variety of reagents such as $(MeO)_2P(O)CO_2Me$, $(CF_3CH_2O)_2P(O)CO_2Me$, and $Ph_3PCH_2CO_2Me$ were used but Mayer–Schuster rearrangement[18] was found to be effective. First the carbonyl compound **24** was treated with lithiated ethyl ethynyl ether in THF at −78 °C followed by Mayer–Schuster rearrangement, using anhydrous $AuCl_3$ in $CH_2Cl_2$–EtOH solvent system at room temperature to afford **25**, as an inseparable mixture of *E* and *Z* olefins (3.4:1), in 61% yield in two steps. Then this inseparable mixture of compounds was treated with *m*-CPBA in $CH_2Cl_2$ at 0 °C to give the *E* olefinic epoxy compound **20** (single diasteromer) in 65% yield. The stereochemistry of the epoxy ring was not determined as its opening with Ti(III) was expected to lead to a radical center. The minor *Z*-isomer **26** could be separated easily at this stage through silica gel column chromatography. The *E* geometry of **20** was confirmed from NOE experiment. $^1$H NOE study showed that irradiation of the olefinic singlet signal at $\delta$ 5.59 caused no enhancement of the proton signal at $\delta$ 2.18 corresponding to allylic methyl. Similarly on irradiation of allylic methyl singlet signal at $\delta$ 2.18, there was no enhancement of proton signal at $\delta$ 5.59 corresponding to olefinic proton. On the other hand, irradiation of the olefinic singlet signal at $\delta$ 5.6 enhanced the peak of allylic C$H_2$ quatrate at $\delta$ 2.1 to prove the *E* geometry of **20**. To carry out the crucial radical-mediated cyclization reaction, the epoxy alcohol **20** was treated with $Cp_2TiCl$[1] (generated in situ using $Cp_2TiCl_2$, $ZnCl_2$, and activated Zn powder) in THF at −20 °C, then allowed to come to room temperature and stirred for another 12 h. This metal-mediated radical cyclization gave **27**[19] in 82% yield.

The relative stereochemistry of the newly generated centre was confirmed by NOESY experiment. NOESY spectrum of **27** showed a strong dipolar coupling between $C_8$–H and 10-$CH_3$ indicating that they are in the same side of the cyclic ring. Similarly NOE cross peaks between $C_8$–H/$C_{11}$–H, 10-$CH_3$/$C_{11}$–H proved that $C_{11}$–H also to be in the same side of the bicyclic ring. Stereochemistry of $C_6$–H center was fixed from the NOE between $C_6$–H/$C_9$–H (Fig. 2).

The Ti(III)-mediated ring closure reaction of **20** was expected to provide the desired compound **19** in the same way as **3** was transformed into **4** carrying the $CH_2OH$ and $CH_2CO_2Et$ substituents in cis orientations in the newly formed five-membered ring. But the formation of the unwanted isomer **27**[19], contrary to our expectation, has now given us a challenge to find a way out to access the right intermediate **19** in order to complete the total synthesis of penifulvins.

## Acknowledgments

The authors wish to thank DST, New Delhi for the Ramanna Fellowship (SR/S1/RFOC-06/2006; T.K.C.) and CSIR, New Delhi for research fellowships (A.K.C. and R.S.).

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10. *Spectral data of compound* **11**: $R_f$ = 0.6 ($SiO_2$, 25% EtOAc in petroleum ether); $[\alpha]_D^{28}$ +15.3 (*c* 0.063, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.1 (Me9), 1.32 and 1.44 (acetonide methyls), 1.36 (m, H4′), 1.43 (m, H7), 1.75 (m, H4), 2.02 (m, H5′), 2.12 (m, H5), 2.47 (d, $^3J_{2\text{-}2'}$ = 14.7 Hz, H2), 2.79 (d, $^3J_{2\text{-}2'}$ = 14.7 Hz, H2′), 3.64 (s, 3H), 3.80 (dd, $^3J_{8\text{-}8'}$ = 12.5 Hz, $^3J_{7\text{-}8'}$ = 3.2 Hz, H8′), 4.06 (dd, $^3J_{8\text{-}8'}$ = 12.5 Hz, $^3J_{7\text{-}8}$ = 5.4 Hz, H8), 4.43 (dt, *J* = 1.4, 6.1 Hz, H6); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 173.3, 97.2, 72.4, 57.9, 51.0, 48.3, 47.8, 41.0, 36.7, 31.1, 30.1, 28.7, 26.2; IR (KBr): 2983, 2859, 1727, 1427, 1178 cm$^{-1}$; MS (ESI): *m/z* 265 (20) $[M+Na]^+$.
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19. *Synthesis of compound* **27**: To a stirred solution of $ZnCl_2$ (1.07 g, 8.51 mmol) in THF (60 mL) were added activated Zn dust (1.11 g, 17.02 mmol) and $Cp_2TiCl_2$ (2.1 g, 8.51 mmol) sequentially at room temperature. The stirring was continued for another 1 h and cooled to −20 °C. Then compound **20** (800 mg, 2.83 mmol) in THF (10 mL) was added drop by drop to the stirred solution of $Cp_2TiCl$ generated in situ. The reaction mixture was warmed up to room temperature over a period of 1 h and stirring was continued for additional 12 h. The reaction was then quenched with saturated $NH_4Cl$ solution (5 mL) and filtered through Celite. The filtrate was diluted with EtOAc (100 mL), washed with water (20 mL), brine (20 mL), and dried over anhydrous $Na_2SO_4$. The organic extract was concentrated in vacuo and chromatographed on silica gel with EtOAc–petroleum ether (1:4) as eluant to afford **27** (659 mg, 82%) as colorless oil. $R_f = 0.3$ ($SiO_2$, 25% EtOAc in petroleum ether); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 4.40 (t, $J = 8.1$ Hz, 1H), 4.31 (q, $J = 7.3$ Hz, 2H), 3.94 (d, $J = 12.5$ Hz, 1H), 3.82 (d, $J = 12.5$ Hz, 1H), 3.51 (br s, 1H), 2.86 (d, $J = 14.7$ Hz, 1H), 2.59 (d, $J = 14.7$ Hz, 1H), 2.36–2.16 (m, 2H), 1.87 (d, $J = 13.9$ Hz, 1H), 1.83 (d, $J = 2.1$ Hz, 1H), 1.78–1.67 (m, 2H), 1.64 (br s, 1H), 1.63 (d, $J = 13.9$ Hz, 1H), 1.56–1.46 (m, 1H), 1.29 (s, 3H), 1.26 (t, $J = 7.3$ Hz, 3H), 1.04 (s, 3H), 0.87 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 174.4, 78.2, 65.9, 63.1, 60.4, 56.8, 55.5, 44.4, 37.5, 34.0, 33.9, 28.7, 24.2, 21.4, 14.2; IR (neat): 3435, 2959, 1733, 1717, 1457, 1370, 1217 $cm^{-1}$; MS (ESI): $m/z$ 285.7 (100) $[M+H]^+$.