Tetrahedron Letters 52 (2011) 3275–3278

Contents lists available at ScienceDirect

Tetrahedron Letters

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

First total synthesis of tenuifolin via PIFA mediated oxidative biaryl coupling

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ARTICLE INFO

Article history:
Received 15 March 2011
Revised 6 April 2011
Accepted 11 April 2011
Available online 22 April 2011

Keywords:
Total synthesis
Tenuifolin
Oxidative biaryl coupling
Wittig coupling
Antitumor

ABSTRACT

The first total synthesis of a sesquiterpenoid, tenuifolin, was achieved in seven linear steps. Phenyliodine(III) bis(trifluoacetate) (PIFA) mediated oxidative biaryl coupling was employed as a key step to construct the central seven-membered ring with a double bond. The double bond formation was also exploited.

Biaryl compounds bearing 6, 7, 6-ring system were found in a variety of natural products and synthetic pharmaceuticals, such as alkaloids, as well as cyclolignans (Fig. 1).[1] Several of these compounds have been proved to be active against many cancer cell lines. For example, allocolchicine (**1**), derived from Colchicine (**2**), could bind to the cytoskeletal protein tubulin, disrupting the microtubule-dependent functions in the cell and thereby suppressing the cell division process.[2] The tricyclic core with a central seven-membered B ring has generally been known to play an important role in bioactivity. Recently, Lin et al. isolated a new sesquiterpenoid, tenuifolin (**4**) from the stems of *Cinnamomum tenuifolium*.[3] Extensive 2D-NMR experiments elucidated the structure of **4**, showing that **4** contains an additional double bond on B-ring. Although **4** was found to bear a similar scaffold as allocolchicine, a preliminary bioassay indicated that **4** only displayed weak antiproliferative activity against tumor cell line DU145.[3] The interesting structure of **4** and the difference in biological activity between **4** and other compounds bearing 6, 7, 6-ring system promote us to initiate the total synthesis of **4** for further pharmacological study.

Due to their remarkably unique structural features and interesting bioactive properties, these natural products have attracted synthetic and medicinal chemists for several decades and the total synthesis of several related compounds have been achieved.[1a] The key step of most synthetic strategies was the construction of the central B ring at a late stage. In recent years, many approaches have been developed toward the synthesis of the B ring, such as palladium catalyzed direct C–H arylation for **1** and its analog,[4] intramolecular thallium(III) trifluoroacetate-mediated non-phenolic oxidative cyclization for (−)-*N*-acetylcochinol,[5] siloxane coupling-ring expansion route to racemic *N*-acetylcochinol-*O*-methyl ether (racemic NSC 51046)[6] and intramolecular Nicholas reaction for enantiomerailly pure NSC 51046.[7] About two decades ago, Kita et al. reported an elegant oxidative biaryl coupling reaction using $PhI(OCOCH_3)_2$, (PIDA), or (PIFA) as an oxidant.[8] This method is

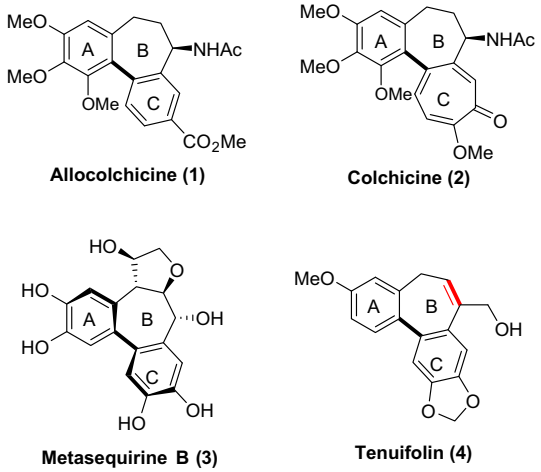

Figure 1. Structures of naturally occurring biaryl molecules.

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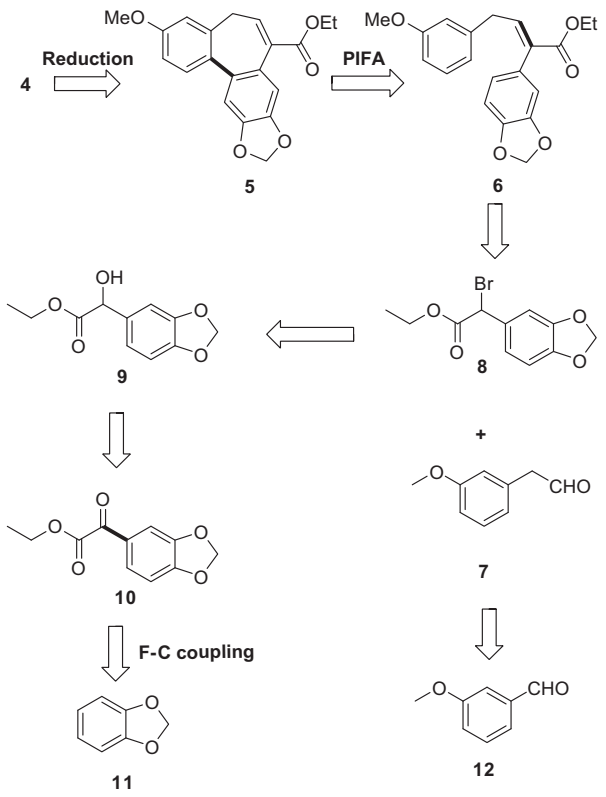
doi:10.1016/j.tetlet.2011.04.069



Scheme 1. Retrosynthetic analysis of tenuifolin (**4**).

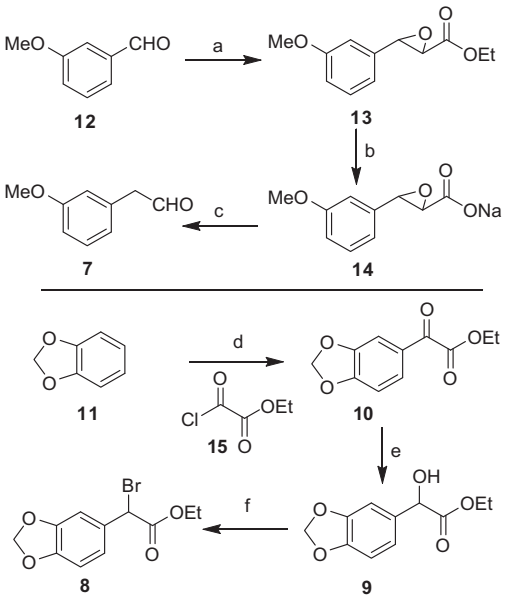
rather atom economic and has been successfully applied to the synthesis of various biaryl molecules.[9] Herein we wish to describe the first total synthesis of **4** using this strategy.

Our initial retrosynthetic analysis of **4** is outlined in Scheme 1. Compound **4** could be readily prepared via a reduction of ester **5**. We envisioned that the biaryl scaffold of **5** could be constructed at late stage using PIFA mediated oxidative biaryl coupling from ester **6**, which, in turn, would be acquired through a coupling reaction between aldehyde **7** and bromoester **8**. Finally, **8** could be derived from commercially available benzodioxole **11**.

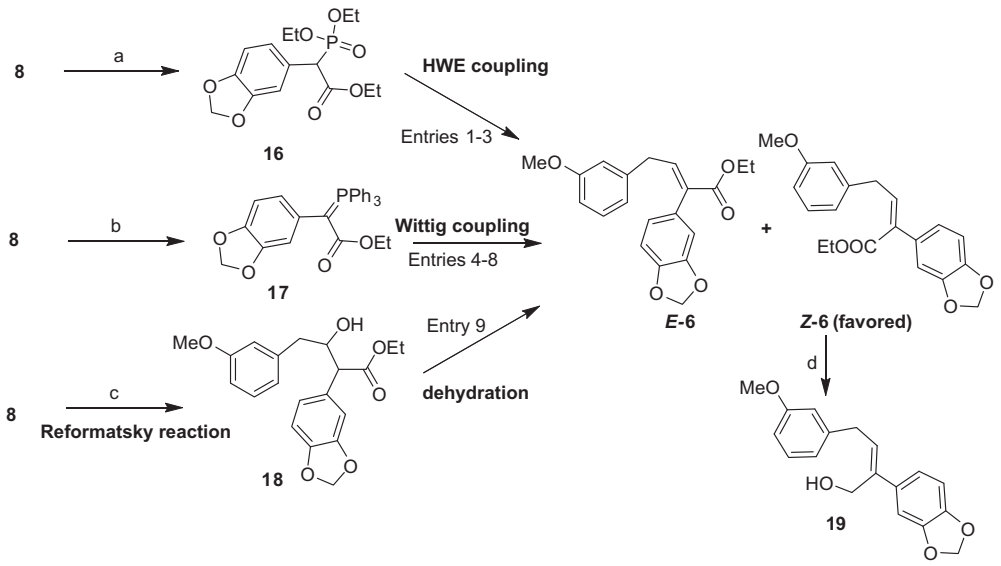
The synthesis of two fragments, aldehyde **7** and bromoester **8**, was depicted in Scheme 2. A Darzens condensation between benzaldehyde (**12**) and $ClCH_2COOEt$ and sequential treatment with aqueous NaOH, followed by HCl smoothly furnished fragment **7** (55% over three steps). A Friedel–Crafts acylation of benzodioxole **11** using ethyl 2-chloro-2-oxoacetate (**15**) (92%), followed by reduction using $NaBH_4$ (98%) and a bromination using PBr_3 (72%) afforded fragment **8** in good yield.[10]

With fragments **7** and **8** in hand, we focused our attention on the coupling reaction between them to generate the double bond as shown in Scheme 3 and Table 1. First, we tried intermolecular Horner–Wadsworth–Emmons (HWE) reaction. Thus, phosphono ester **16** was prepared from **8** and distilled $P(OEt)_3$ via Michaelis–Arbuzov reaction in 98% yield. It was reported that the condensation of **16** and benzaldehyde could produce the olefination product in moderated yield with high *E*-selectivity.[10] However, our initial attempts of HWE reaction between **16** and phenylacetaldehyde **7** under DBU/LiCl in THF at room temperature only gave the desired **6** in low yield with poor *E*-selectivity (Table 1, entry 1). The mixture of *E*-**6** and *Z*-**6** was inseparable by flash chromatography. We then examined the reaction conditions by changing base and solvent and found that the total yield of **6**, as well as the *E*-selectivity was not yet well improved (Table 1, entries 2 and 3). Next, we tried Wittig reaction in neutral condition. Treatment of **8** with PPh_3 in anhydrous toluene and subsequently basification with aqueous NaOH provided the Wittig reagent **17**. Unfortunately, Wittig coupling between **7** and **17** at low or elevated temperature also afforded *Z*-**6** (*E*:*Z* = 1:5.3–1:14) as a major product. These results clearly indicated that higher temperature or loading of **17** favored the formation of the *Z*-isomer (Table 1, entries 4–8).[11] The configuration of double bond of *Z*-**6** was confirmed by ROESY analysis of alcolol **19**, which was reduced from *Z*-**6** by DIBAL-H. Finally, we tried the Reformatsky reaction-dehydration to generate the double bond. Treatment of **8** with activated Zn powder in THF and coupling with **7** afforded β-hydroxyester **18** in 90% yield. Elimination of the hydroxyl group of **18** with MsCl in CH_2Cl_2 at room temperature for 12 h proceeded smoothly to afford **6** in 89% yield with slightly improved *E*-selectivity (*E*:*Z* = 1:2) (Table 1, entry 9).

After we successfully achieved the desired product **6**, we next investigated the PIFA mediated biaryl coupling reaction. Thus, treatment of the mixture of **6** (*E*:Z = 1:2) with 1.0 equiv of PIFA in the presence of BF_3–Et_2O at −45 °C for 4–6 h (Scheme 4) successfully furnished the corresponding product **5** in 56% isolated yield.[12] Very interstingly, *E*-**6** and most of *Z*-**6** were found to be consumed after 4 h. According to Dominguez's report[13] that the proximity of two aromatic rings is needed for this biaryl coupling, theoretically, our reaction should give the desired product in less than 33% yield. Therefore, we presumed that *Z*-**6** might undergo the isomerization to *E*-**6,** which subsequently converted to **5**, rendering the higher yield than the theoretical one. The isomerization was indeed observed when *Z*-**6** was treated with BF_3–Et_2O or PIFA in CH_2Cl_2 at low temperature. Encouraged by this result, we further used the mixture of **6** (*E*:Z = 1:14) for the coupling reaction. Indeed, the desired product **5** could be achieved in 45–58% yield (see Supplementary data S1). Finally, the ester **5** was reduced with DIABL-H in THF at −78 °C to afford tenuifolin **4** in excellent yield (91%, Scheme 4). The structure of **4** was confirmed by ^1H NMR, ^{13}C NMR, IR, and HR-MS (ESI).[14] NOESY analysis of 4 clearly indicated the *E*-configuration of double bond on B ring. The spectroscopic data of synthetic tenuifolin (**4**) were identical to those of an authentic sample reported in the literature.



Scheme 2. Synthesis of fragments **7** and **8**. Reagents and conditions: (a) $ClCH_2COOEt$, EtONa, EtOH, 15–20 °C; (b) NaOH, H_2O, 15–20 °C; (c) NaH_2PO_4, HCl, H_2O, rt (55% over three steps); (d) $AlCl_3$, CH_2Cl_2, 0 °C (92%); (e) $NaBH_4$, EtOH, −20 °C (98%); (f) PBr_3, CH_2Cl_2, 0 °C (72%).

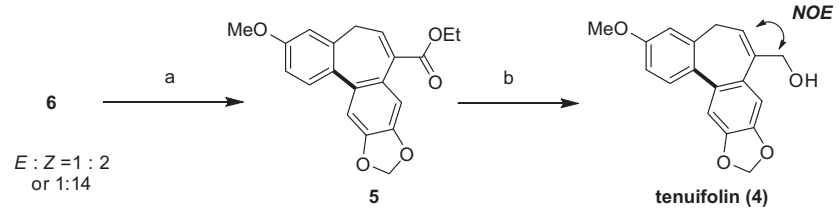


Scheme 3. Reagents and conditions: (a) distilled $P(OEt)_3$, reflux, 6 h, (98%); (b) Ph_3P, anhydrous toluene, 70 °C, overnight; then aq NaOH (88%); (c) Zn powder, anhydrous THF, rt then **7**, rt to reflux, 2 h (90%); (d) DIBAL-H, THF, −78 °C, 92%.

Table 1
The formation of the double bond on B-ring under various conditions

Entry	Condition	Yield[a] (%) (**6**)	Ratio[b] (*E*:*Z* by ^{1}H NMR)
1	DBU, LiCl, CH_3CN, then **7**, rt	16	1:2.0
2	NaH, THF, then **7**, rt	24	1:4.0
3	BuOK, THF, LiCl, then **7**, rt	29	1:3.3
4	1.0 equiv of **17**, toluene, rt	Trace	—
5	1.5 equiv of **17** + 1.0 equiv of **7**, toluene, 50 °C, 36 h	11	1:3.6
6	1.0 equiv of **17** + 1.0 equiv of **7**, toluene, 90 °C, 36 h	35	1:5.3
7	1.5 equiv of **17**+1.0 equiv of **7**, toluene, 90 °C, 36 h	75	1:12.0
8	2.0 equiv of **17** + 1.0 equiv of **7**, toluene, 90 °C, 36 h	89	1:14.0
9	MsCl, NEt_3, DBU, CH_2Cl_2, 0 °C to rt, 12 h	89	1:2.0

[a] Total isolated yields (*E*-**6** + *Z*-**6**) after flash chromatography.
[b] Determined by ^{1}H NMR.



Scheme 4. The synthesis of tenuifolin (**4**). Reagents and conditions: (a) PIFA (1 equiv), BF_3–Et_2O (1 equiv), CH_2Cl_2, −45 °C, 45–58%; (b) DIBAL-H, THF, −78 °C, 91%.

In conclusion, the first total synthesis of tenuifolin in seven linear steps without any protecting group was successfully achieved using readily available starting materials. The synthetic route is highlighted by the oxidative biaryl coupling reaction to construct a seven-membered B ring bearing a double bond. Efforts on the application to the synthesis of other related natural products and the structural modification of tenuifolin for further pharmacological study are undergoing in our laboratory and will be reported in due course.

Acknowledgments

Financial support the National Natural Science Foundation (No. 20902111), Program for New Century Excellent Talents in University (NCET 2008) by the Ministry of Education of China, 2009ZX09103-128 and Fundamental Research Funds for the Central Universities (JKZ2009002 for H.Y.) are highly appreciated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.069.

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11. *Z*-**6**: coloress oil; IR (KBr) 2985, 2938, 2896, 2831, 1711, 1600, 1584, 1503, 1489, 1437, 1369, 1259, 1235, 1149, 1101, 1038, 935, 865, 812, 764, 749, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.11 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.77-6.67 (m, 5H), 5.98 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.41 (d, J = 7.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 159.8, 147.4, 147.1 142.2, 140.4, 134.2, 129.7, 128.6, 123.3, 120.9, 114.4, 111.6, 110.3, 108.1, 101.1, 61.0, 55.2, 35.7, 14.3; ESI-MS m/z 341.2 $[M+H]^+$; HR-MS(ESI) m/z calcd for $C_{20}H_{20}O_5$: 340.1318; found: 340.1305.
12. *Ester* **5**: white solid; mp 97–99 °C; IR (KBr) 2958, 2924, 2843, 1710, 1607, 1501, 1483, 1433, 1309, 1273, 1256, 1233, 1178, 1154, 1122, 1097, 1042, 933, 868, 815, 771, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.52 Hz, 1H), 7.27 (t, J = 6.5 Hz, 1H), 7.05 (s, 1H), 7.02 (s, 1H), 6.85 (q, J = 2.3 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.01 (d, J = 4.0 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.22 (dd, J = 12.1, 8.4 Hz, 1H), 2.84 (dd, J = 12.1, 7.0 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.3, 146.9, 145.7, 141.7, 140.1, 134.8, 131.3, 130.9, 130.5, 126.6, 112.2, 111.9, 109.6, 108.9, 101.2, 60.9, 55.3, 33.6, 14.2; EI-MS m/z 339.2 $[M^+]$; HR-MS(ESI) m/z calcd for $C_{20}H_{18}O_5$: 338.1157; found: 338.1148.
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14. *Tenuifolin* (**4**): white solid; mp 116–119 °C; IR (KBr) 3319, 2961, 2924, 2861, 1720, 1606, 1501, 1483, 1401, 1307, 1275, 1258, 1231, 1154, 1121, 1039, 930, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.5 Hz, 1H), 7.13 (s, 1H). 7.07 (s, 1H), 6.83 (q, J = 2.5 Hz, 1H), 6.76 (d, J = 2.2 Hz, 1H), 6.16 (t, J = 7.1 Hz, 1H), 6.02 (d, J = 1.9 Hz, 2H), 4.48 (d, J = 12.8 Hz, 1H), 4.32 (d, J = 12.8 Hz, 1H), 3.83 (s, 3H), 3.08 (dd, J = 12.6, 8.2 Hz, 1H), 2.77 (dd, J = 12.8, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 146.4, 143.6, 137.4, 134.6, 131.2, 130.6, 129.8, 127.6, 111.7, 111.5, 109.5, 106.0, 101.2, 66.1, 55.3, 33.1; EI-MS m/z 297.2 $[M+H]^+$; HR-MS(ESI) m/z calcd for $C_{18}H_{16}O_4$: 296.1052; found: 296.1043.