Tetrahedron Letters 52 (2011) 581–583

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Total synthesis of (+)-eupomatilone 2 via asymmetric [2,3]-Wittig rearrangement of highly oxygenated biphenylmethyl ethers

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ARTICLE INFO

Article history:
Received 29 October 2010
Revised 22 November 2010
Accepted 24 November 2010
Available online 27 November 2010

Keywords:
Asymmetric synthesis
Natural product
[2,3]-Wittig rearrangement
Bis(oxazoline) ligand

ABSTRACT

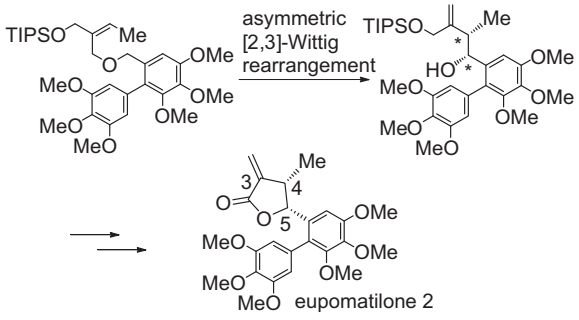
We have achieved the total synthesis of (±)- and (+)-eupomatilone 2 isolated from the Australian shrub *Eupomatia bennettii*. The key reaction was an asymmetric [2,3]-Wittig rearrangement employing a bis(oxazoline) chiral ligand. Although the highly oxygenated biphenylmethyl ether exhibited considerably lowered enantioselectivity as compared with the non-substituted biphenylmethyl ether, the selectivity was improved to 89% ee by using *n*-BuLi and ether as the base and the co-solvent, respectively.

1. Introduction

In 1991, structurally unique lignans named eupomatilones were isolated from the Australian shrub *Eupomatia bennettii* by Carroll and Taylor. This degraded lignan possesses an oxygenated biaryl skeleton with a γ-lactone ring constructed via the rearrangement of a dimeric phenylpropane precursor.[1] Eupomatilone 2 is a congener having six methoxy groups and is characterized by an α-methylene-γ-lactone group, which is expected to interact with biomolecules. Although many syntheses of congeners bearing a saturated C3 substituent have been reported,[2] there are few total syntheses of this natural product. Examples include synthesis of the racemate by using an allylindium reagent[3] and an asymmetric synthesis by using a chiral carbomethoxycrotyl boronate reagent with moderate enantioselectivity (76% ee).[4]

We were interested in this natural product for its unique structure and unexplored biological activity. We planned to synthesize eupomatilone 2 by employing an asymmetric [2,3]-Wittig rearrangement of arylmethyl ether in the presence of an external chiral ligand (Scheme 1). During preliminary research, we found that the simple biarylmethyl ether rearranged with high enantio- and diastereoselectivity.[5] This success encouraged us to apply this strategy to the synthesis of highly oxygenated biaryl-type natural products.

Herein, we report the enantioselective total synthesis of eupomatilone 2 by employing the asymmetric [2,3]-Wittig rearrangement as the key reaction.



Scheme 1. Synthetic plan of eupomatilone 2.

2. Result and discussion

As shown in Scheme 2, the highly congested biaryl moiety of eupomatilone 2 was constructed using the modified Suzuki coupling of 2-bromo-3,4,5-trimethoxybenzyl alcohol **1**[6] and 3,4,5-trimethoxyphenylboronic acid **2,** utilizing the *o*-(dicyclohexylphosphine)biphenyl ligand, as developed by Buchwald.[7] The coupling reaction proceeded smoothly to give the biaryl product **3** in 76% yield [$Pd(OAc)_2$, (*c*-Hex)$_2$(Biphenyl)P, K_3PO_4, toluene, at 80 °C]. The resulting alcohol **3** underwent the Williamson ether synthesis with allylic bromide **4**[5] in the presence of *t*-BuOK, giving the biarylmethyl ether **5** in 71% yield.

After obtaining the required substrate **5**, we investigated the [2,3]-Wittig rearrangement with *t*-BuLi (5 equiv) in THF at

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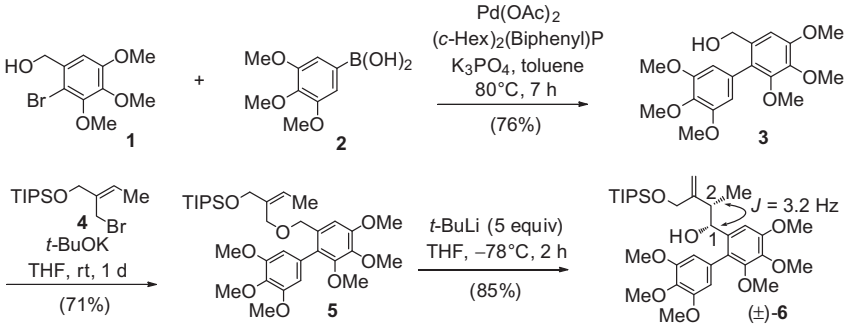
doi:10.1016/j.tetlet.2010.11.126



Scheme 2. Synthesis of alcohol (±)-**6**.

−78 °C. Fortunately, regioselective deprotonation proceeded predominately at the benzylic position in the presence of allylic protons, and the [2,3]-Wittig rearranged product (±)-**6** was obtained in 85% yield. Formation of the [1,2]-Wittig rearranged product was not observed.

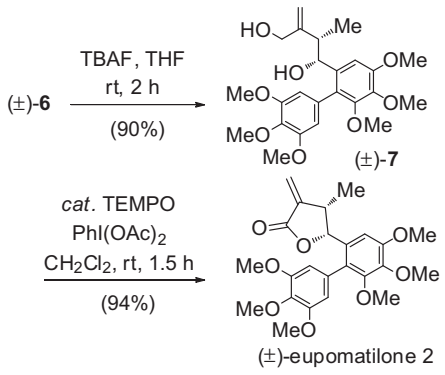
The reaction afforded a sole diastereoisomer, and the relative stereochemistry of the resulting alcohol (±)-**6** was assumed to be a *syn* relationship based on the coupling constant between the two methine protons at the C1 and C2 positions (J = 3.2 Hz).[8]

The total synthesis of (±)-eupomatilone 2 in 85% yield was accomplished in two steps by deprotecting the TIPS group with TBAF and subsequent primary alcohol selective TEMPO oxidation in the presence of $PhI(OAc)_2$ as a co-oxidant[9] (Scheme 3). Spectral data (IR, ^1H and ^{13}C NMR) were consistent with those reported for the natural product.[1,4]

Next, we examined the asymmetric [2,3]-Wittig rearrangement of **5** by using bis(oxazoline) as an external chiral ligand.[10] The results are summarized in Table 1.

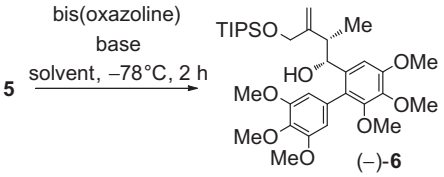
The reactions were performed using 1 equiv of the chiral ligand and 5 equiv of the base at −78 °C for 2 h. The enantiomeric excess was significantly dependent on the structure of the bis(oxazoline) ligand (Fig. 1). Bulkiness at the C4 position was important to achieve high ee (entries 1 and 2), but bulkiness at the C5 position and on the methylene bridge reduced both the yield and enantioselectivity (entries 3–5). The ligand **L1** achieved the best yield and selectivity, although ee was moderate (68% ee). It is in sharp contrast that the simple biphenylmethyl ether with no methoxy substituent showed excellent selectivity (92% ee).[5]

We observed that the highly oxygenated substrate slowly underwent the [2,3]-Wittig rearrangement even with bases weaker than *t*-BuLi. To our delight, *s*-BuLi and *n*-BuLi exhibited better enantioselectivity than *t*-BuLi but in reduced yield (entries 6 and 7). The yield improved to 77% when the reaction progressed for 4 h (entry 8). Interestingly, the addition of toluene as a co-solvent accelerated the reaction time and the reaction was completed within 2 h. The rearranged product (−)-**6** was obtained in 92% yield



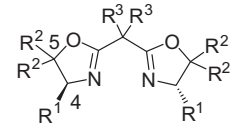
Scheme 3. Synthesis of racemic eupomatilone 2.

Table 1
Asymmetric [2,3]-Wittig rearrangement of **5**



Entry	Conditions[a]	Yield[b] (%)	ee[c] (%)
1	**L1**, *t*-BuLi, hexane	92	68
2	**L2**, *t*-BuLi, hexane	72	38
3	**L3**, *t*-BuLi, hexane	0	—
4	**L4**, *t*-BuLi, hexane	38	22
5	**L5**, *t*-BuLi, hexane	43	12
6	**L1**, *s*-BuLi, hexane	50	71
7	**L1**, *n*-BuLi, hexane	46	77
8	**L1**, *n*-BuLi, hexane[d]	77	77
9	**L1**, *n*-BuLi, hexane/toluene (4/1)	92	80
10	**L1**, *n*-BuLi, hexane/ether (4/1)	98	89
11	**L1**, *n*-BuLi, hexane/ether (1/1)	83	89
12	**L1**, *n*-BuLi, hexane/THF (4/1)	7	5

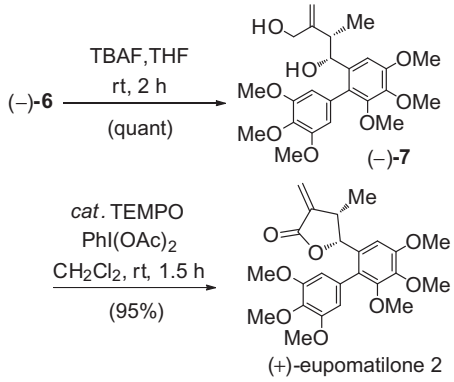
[a] The reactions were carried out in the presence of chiral ligand (1 equiv) and base (5 equiv) in dry solvent at −78 °C for 2 h under Ar atmosphere unless stated otherwise.
[b] Isolated yield.
[c] Determined by chiral HPLC (Column: CHIRALPAK AD-H, solvent: hexane–*i*-PrOH = 98:2, flow rate: 1 mL/min).
[d] The reaction was carried out for 4 h.



L1: R^1=*t*-Bu, R^2=H, R^3=Me
L2: R^1=*i*-Pr, R^2=H, R^3=Me
L3: R^1=*t*-Bu, R^2=Me, R^3=Me
L4: R^1=*i*-Pr, R^2=Me, R^3=Me
L5: R^1=*t*-Bu, R^2=H, R^3=Et

Figure 1. Chiral bis(oxazoline) ligands **L1**–**L5**.

with 80% ee (entry 9). Finally, when ether was added as a co-solvent, both the yield and enantioselectivity were optimized up to 98% and 89% ee, respectively (entry 10).[11] The selectivity did not further improve even on increasing the ratio of ether (entry 11). In contrast, addition of the more polar THF suppressed the reaction significantly and both the yield and selectivity decreased dramatically (entry 12). Presumably, the addition of THF interfered with



Scheme 4. Conversion to (+)-eupomatilone 2.

the coordination of the chiral ligand to *n*-BuLi that prevented the formation of a reactive chiral base.

We attempted to confirm the absolute configuration at the chiral center of the secondary alcohol by using the modified Mosher method,[12] but the arbitrary distribution of the $\Delta\delta^{SR}$ sign made the appropriate assignment difficult.[13] The modified Mosher method was, therefore, considered unsuitable for this compound. Consequently, we abandoned our attempt to confirm the absolute configuration at this stage and decided to determine it by derivatization of the natural product.

Finally, we transformed the product (−)-**6** into chiral eupomatilone 2, as shown in Scheme 4. After deprotecting the TIPS group with TBAF, the resulting diol (−)-**7** was selectively oxidized using catalytic TEMPO in the presence of $PhI(OAc)_2$ as co-oxidant.[9] Thus, (+)-eupomatilone 2 in 95% yield was obtained in two steps.[14,15] The sign of specific rotation was reversed on the formation of γ-lactone. Thus, the sign of the synthetic eupomatilone 2 matched that of the natural product; however, its value was greater than that reported in literature [$[\alpha]_D^{25}$ +12.0 (*c* 0.60, $CHCl_3$); lit. $[\alpha]_D$ +3.3 (*c* 0.5, $CHCl_3$)].[1] The ^1H and ^{13}C NMR spectra were identical to those in the reported data.[1,4]

In conclusion, we have achieved the total synthesis of (±)- and (+)-eupomatilone 2 by employing a [2,3]-Wittig rearrangement as the key reaction. We optimized the enantioselectivity up to 89% ee by using the bisoxazoline ligand **L1** and *n*-BuLi in a solvent mixture of *n*-hexane and ether, and obtained (+)-eupomatilone 2 in 50% overall yield from alcohol **1** in five steps. This strategy contributes to our knowledge of the synthesis of eupomatilone congeners and their derivatives as well as related biological research. The application of this method to other congeners will follow in due course.

Acknowledgments

We acknowledge the financial support of the Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (No. 21590032) and the Osaka Ohtani University Research Fund (Pharmaceutical Sciences).

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11. Procedure of asymmetric [2,3]-Wittig rearrangement (Table 1, entry 10). *n*-BuLi (1.6 M in hexane, 1.25 mL, 2.00 mmol) was added dropwise to a suspension of ether **5** (240 mg, 0.40 mmol) and bis(oxazoline) ligand **L1** (118 mg, 0.40 mmol) in a 4:1 mixture of dry hexane and dry ether (2 mL) with stirring at −78 °C under Ar. The stirring continued at this temperature for 2 h. The reaction was quenched with saturated NH_4Cl (8 mL) and the mixture was partitioned between EtOAc (40 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL). Prior to drying and solvent evaporation, the combined organic layer was washed with water (20 mL) and brine (20 mL). The residue was chromatographed on silica gel with hexane–EtOAc (3:1) to give alcohol (−)-**6** (235 mg, 98%, 89% ee) as a colorless oil. $[\alpha]_D^{25}$ −21.2 (*c* 0.72, $CHCl_3$); ^1H NMR δ: 0.96 (d, *J* = 7.1 Hz, 3H), 1.00–1.10 (21H), 2.35 (qd, *J* = 7.1, 3.2 Hz, 1H), 3.50 (br, 1H), 3.67 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.82 (d, *J* = 12.7 Hz, 1H), 3.89 (s, 6H), 3.93 (s, 3H), 4.03 (d, *J* = 12.7 Hz, 1H), 4.52 (s, 1H), 4.77 (d, *J* = 3.2 Hz, 1H), 4.97 (d, *J* = 1.2 Hz, 1H), 6.42 (d, *J* = 1.7 Hz, 1H), 6.47 (d, *J* = 1.7 Hz, 1H), 7.04 (s, 1H); ^{13}C NMR δ: 11.16, 11.85 (3C), 17.85 (6C), 43.80, 55.93, 55.97, 56.16, 60.77, 60.84, 61.25, 65.09, 72.61, 105.74, 106.59, 108.01, 113.05, 127.31, 131.92, 136.39, 136.94, 140.86, 150.51, 150.96, 152.39, 152.79, 153.00; IR (KBr) cm^{-1}: 3477, 3097, 1586; MS (FAB) *m/z*: 605 $[M+H]^+$; HRMS (FAB) *m/z*: calcd for $C_{33}H_{52}O_8Si$: 605.3510, found: 605.3528 $[M+H]^+$.
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14. The enantiomeric excess of the synthetic (+)-eupomatilone 2 was confirmed as 89% ee by chiral HPLC (Column: CHIRALPAK AD-H, solvent: hexane–*i*-PrOH = 9:1, flow rate: 1 mL/min).
15. Spectral data of synthetic (+)-eupomatilone 2: $[\alpha]_D^{23}$ +12.02 (*c* 0.60, $CHCl_3$); ^1H NMR δ: 0.84 (d, *J* = 7.3 Hz, 3H), 2.88 (qnt, *J* = 7.3, 2.1 Hz, 1H), 3.70 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.92 (s, 6H), 5.52 (d, *J* = 7.3 Hz, 1H), 5.55 (d, *J* = 2.0 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 6.37 (d, *J* = 1.7 Hz, 1H), 6.46 (d, *J* = 1.7 Hz, 1H), 6.69 (s, 1H); ^{13}C NMR δ: 16.86, 38.31, 56.12, 56.16, 56.25, 60.88, 60.92, 61.37, 79.26, 104.86, 106.42, 107.42, 122.07, 127.64, 129.86, 131.01, 137.28, 140.90, 141.90, 151.25, 152.98, 153.06, 153.24, 170.14; IR (KBr) cm^{-1}: 3097, 1767, 1664, 1592; MS (FAB): *m/z* 445 $[M+H]^+$; HRMS (FAB): *m/z* calcd for $C_{24}H_{28}O_8$: 445.1862, found: 445.1853 $[M+H]^+$.