Tetrahedron Letters 51 (2010) 1979–1981

Contents lists available at ScienceDirect

Tetrahedron Letters

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

An expeditious and convergent synthesis of ailanthoidol

Maddali L. N. Rao *, Dheeraj K. Awasthi, Debasis Banerjee

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208 016, India

ARTICLE INFO

Article history:
Received 21 December 2009
Revised 27 January 2010
Accepted 5 February 2010
Available online 8 February 2010

Keywords:
Convergent
Ailanthoidol
Wittig
Expeditious
Concise synthesis

ABSTRACT

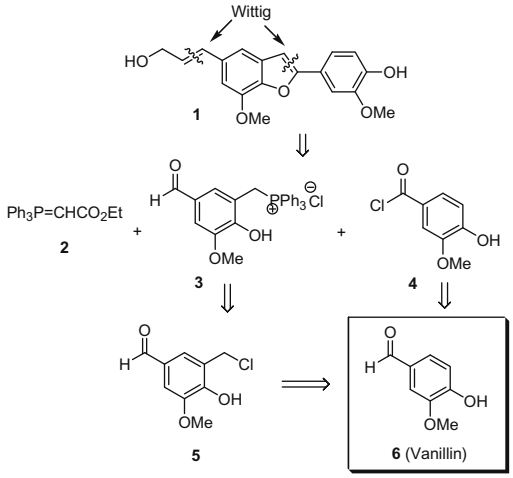
An expeditious and concise method has been described for the synthesis of ailanthoidol through convergent route starting from vanillin. The protocol involving intramolecular Wittig as a key reaction afforded ailanthoidol in overall high yield.

2-Aryl-substituted benzofurans such as ailanthoidol and its structural analogues belong to neolignan family.[1] This class of compounds is known for various biological properties such as antiviral, anticancer, antiproliferative, antioxidative, anti-inflammatory, antifungal and immuno-suppressive.[2a,2b] Recently, some groups have reported the synthesis of ailanthoidol and its analogues.[2,3] For example, a synthesis reported by Chern et al. involves cyclization of internal alkyne through oxymercuration using mercury acetate in acetic acid for the generation of benzofuran core of ailanthoidol (Scheme 1).[2a,2b] Another synthesis by Bates et al. employed the palladium-catalyzed Sonogashira coupling followed by the base-mediated cyclization of alkyne intermediate starting from 5-iodovanillin.[2c] The palladium-catalyzed Stille couplings were involved to introduce 2-aryl group and for the chain extension of benzofuran core, reported by Lee and co-workers.[2d] The 2-bromobenzofuran needed for Stille couplings was derived from 5-bromo-2-hydroxy-3-methoxybenzaldehyde. Other methods involve palladium-catalyzed cyclization,[2e] benzoannulation[2f] and cuprous acetylide coupling[3a–c] along with other procedures[3d,3e] to generate benzofuran skeleton. However, some of these methods despite being useful for the synthesis of ailanthoidol also suffer from the use of toxic tin reagents, mercuric reagents and cumbersome procedures. Given the importance of ailanthoidol and its structural analogues in medicinal chemistry, we describe here an alternate, concise and convergent synthesis of ailanthoidol starting from vanillin.

Our approach was based on the utilization of repetitive aromatic nucleus of ailanthoidol as precursor for its synthesis.

Thus, vanillin was viewed as a suitable structural precursor for the convergent synthesis of benzofuran core using intramolecular Wittig as the key reaction. The retro-synthetic analysis conceived for ailanthoidol is illustrated in Scheme 1. As given, benzofuran skeleton could be easily processed through intramolecular Wittig reaction of phosphonium salt **3** and acid chloride **4**. The phosphonium salt in turn could be obtained from functionalized benzyl chloride **5**. The desired benzyl chloride and acid chloride could be easily prepared from vanillin **6**.

Although, the intermolecular Wittig reaction of phosphorane **2** for chain extension of the benzofuran core was employed befor-



Scheme 1. Retrosynthetic analysis of ailanthoidol

* Corresponding author. Tel./fax: +91 512 2597532.
E-mail address: maddali@iitk.ac.in (M.L.N. Rao).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.018

e,[2a,2b] intramolecular Wittig for the generation of benzofuran core was not adopted in the synthesis of ailanthoidol. It is to be noted that synthetically intramolecular Wittig reaction[4] provides a facile approach for the generation of benzofuran skeleton and has been applied before in several syntheses.[5] Despite this, the convergent approach from vanillin in combination with intramolecular Wittig as illustrated above was not realized so far in ailanthoidol synthesis. If adopted this is expected to provide much simplified route for the synthesis of ailanthoidol in comparison with some of the known methods.[2] So, our synthetic efforts to obtain ailanthoidol are described below.

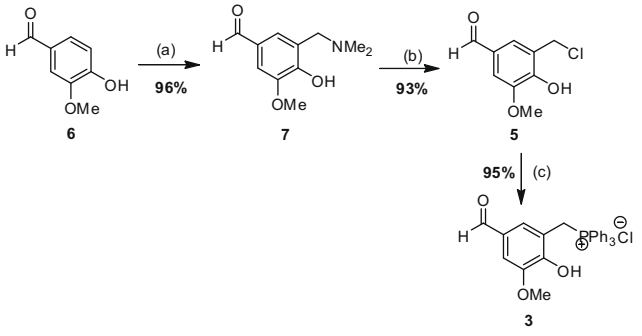
The functionalization of vanillin to benzyl derivative **5** (Scheme 2) through direct halomethylation was attempted initially. The reactions using (i) gaseous hydrogen bromide in acetic acid in the presence of paraformaldehyde[6a,6b] (ii) with formaldehyde in concd hydrochloric acid[6c] were not effective to provide benzyl chloride directly from vanillin. Hence, we have followed the procedure[6d] involving initial aminomethylation to **7** and its further transformation to benzyl chloride **5**. These steps afforded high yields in a facile manner. The benzyl chloride was then converted to the phosphonium salt **3**.

Next, the synthesis of acid chloride **10** was accomplished from vanillin as given in Scheme 3. The phenolic group in vanillin **6** was first protected as its benzyl ether **8**. Oxidation of **8** was carried out using sodium chlorite to obtain the corresponding acid **9**. This was further converted to its acid chloride derivative **10** smoothly in quantitative yield.

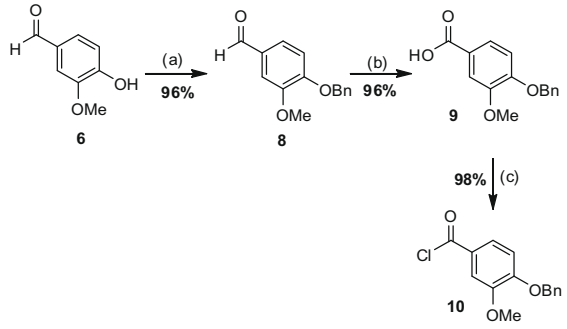
With the two important intermediates phosphonium salt **3** and acid chloride **10** in hand, intramolecular Wittig reaction[4c] was then performed to generate the benzofuran core of ailanthoidol (Scheme 4).

The Wittig reaction of phosphonium salt with acid chloride in the presence of pyridine followed by the treatment of triethylamine under heating condition afforded 2-arylbenzofuran skeleton **11** in high yield.[7] The notable feature of this step is that the formyl group present in phosphonium salt **3** was not protected and the intramolecular Wittig reaction afforded the selective coupling towards benzofuran product.

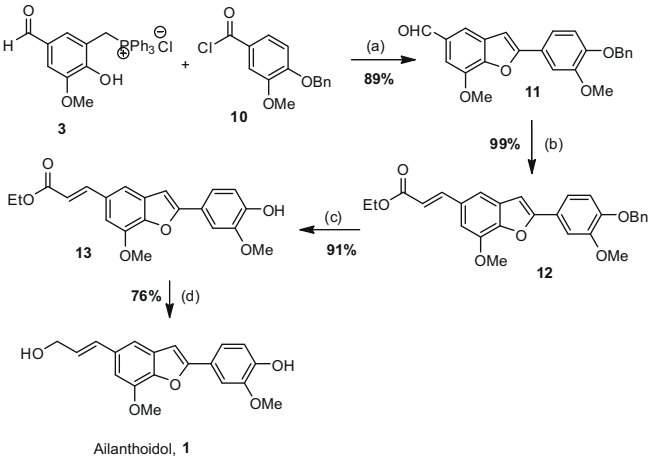
Next, the chain extension of benzofuran core **11** was carried out using intermolecular Wittig reaction with phosphorane **2**. In our initial attempts, this reaction afforded a cis–trans mixture of olefinic ester **12**. To avoid this and to obtain pure *trans*-olefinic ester, we have studied the reaction under different solvent and temperature conditions as they are known to have a role in selectivity.[8] From Table 1, the reaction in toluene,[9a] tetrahydrofuran[2b] and dichloromethane[9b] solvents afforded a mixture of both *cis*- and *trans*-olefinic esters in different amounts (Table 1, entries 1–7). However, in dichloromethane solvent at 0 °C initially followed by room temperature stirring, the reaction afforded *trans*-olefinic ester **12** quantitatively (Table 1, entry 8).[10] Next, debenzylation of the pure *trans*-ester was carried out with $TiCl_4$ to afford olefinic ester **13**.[11] This ester was further subjected to $LiAlH_4/AlCl_3$ reduction to give directly ailanthoidol **1** in high yield.[12] The present synthesis starting from phosphonium salt **3** and acid chloride **10** (Scheme 4) afforded overall 61% yield of ailanthoidol.



Scheme 2. Preparation of phosphonium salt **3**. Reagents and conditions: (a) Me_2NH, HCHO, ethanol, reflux for 0.5 h and rt, 24 h; (b) (i) Ac_2O, reflux 24 h; (ii) conc. HCl, rt 1.5 h; (c) PPh_3, toluene, reflux 4 h.

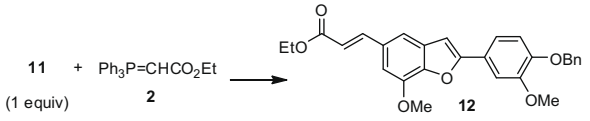


Scheme 3. Preparation of benzyl-protected acid chloride **10**. Reagents and conditions: (a) BnBr, K_2CO_3, DMF, rt, 5 h; (b) H_3NO_3S, $NaClO_2$, H_2O, rt, 12 h; (c) $SOCl_2$, DCM, 1*H*-benzotriazole, rt, 1 h.



Scheme 4. Synthesis of ailanthoidol. Reagents and conditions: (a) (i) $CHCl_3$, pyridine, reflux 2 h; (ii) Et_3N, reflux 6 h; (b) compound **2**, CH_2Cl_2, 0 °C, 3 h and rt, 10 h; (c) $TiCl_4$, CH_2Cl_2, rt, 5 h; (d) $LiAlH_4$, $AlCl_3$, THF, rt, 4 h.

Table 1
Optimizing conditions for **12**[a–c]



Entry	**2** (equiv)	Solvent/temp/time	*E*/*Z* (**12**)	Yield **12** (%)
1	1.5	Toluene, 60 °C,12 h	68:32	50
2	1.5	Toluene, rt	66:34	90
3	1.2	THF, −78 °C, 1 h; rt,3 h	62:38	34
4	1.2	THF, −78 °C, 1 h; 0 °C, 3 h	66:34	53
5	1.2	THF, −78 °C, 3 h	97:3	28
6	1.2	THF, −78 °C, 6 h	84:16	39
7	1.2	DCM, rt, 12 h	99:1	75
8	1.2	DCM, 0 °C, 3 h; rt, 10 h	100:0	99

Conditions: (a) compound **11** (0.3 mmol, 1 equiv), phosphorane **2**, solvent (5 mL). (b) Isolated yields. (c) *E*/*Z* ratio of the isolated product **12** was determined by HPLC.

In conclusion, some highlights of the present synthesis are (a) it involves a convergent route using intramolecular Wittig reaction; (b) efficient utilization of commercially available vanillin as its acid chloride and phosphonium salt derivatives has simplified the overall synthesis; (c) only one benzylic protection was employed throughout the synthesis; (d) majority of the steps were high yielding and by routinely used reagents. So, we have demonstrated an expeditious, convergent and concise synthesis of ailanthoidol by employing precursors derived from vanillin using intramolecular Wittig as the key reaction.

Acknowledgements

D.K.A thanks UGC, New Delhi and D.B. thanks IIT Kanpur for research fellowships.

Supplementary data

Supplementary data (experimental procedures for compounds **3**, **5**, **7**, **8**, **9** and **10** and NMR, mass spectral data for the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.018.

References and notes

1. (a) Sheen, W.-S.; Tsai, I.-L.; Teng, C.-M.; Chen, I.-S. *Phytochemistry* **1994**, *36*, 213–215; (b) Moss, G. P. *Pure Appl. Chem.* **2000**, *72*, 1493–1523.
2. (a) Kao, C.-L.; Chern, J.-W. *Tetrahedron Lett.* **2001**, *42*, 1111–1113; (b) Kao, C.-L.; Chern, J.-W. *J. Org. Chem.* **2002**, *67*, 6772–6787. and references cited therein; (c) Bates, R. W.; Devi, T. R. *Synlett* **1995**, 1151–1152; (d) Lin, S.-Y.; Chen, C.-L.; Lee, Y.-J. *J. Org. Chem.* **2003**, *68*, 2968–2971; (e) Lutjens, H.; Scammells, P. J. *Tetrahedron Lett.* **1998**, *39*, 6581–6584; (f) Fuganti, C.; Serra, S. *Tetrahedron Lett.* **1998**, *39*, 5609–5610.
3. (a) Hutchinson, S. A.; Luetjens, H.; Scammells, P. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3081–3084; (b) Scammells, P. J.; Baker, S. P.; Beauglehole, A. R. *Bioorg. Med. Chem.* **1998**, *6*, 1517–1524; (c) Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248–7257; (d) Bang, H. B.; Han, S. Y.; Choi, D. H.; Yang, D. M.; Hwang, J. W.; Lee, H. S.; Jun, J.-G. *Synth. Commun.* **2009**, *39*, 506–515; (e) Duan, X.-F.; Zeng, J.; Zhang, Z.-B.; Zi, G.-F. *J. Org. Chem.* **2007**, *72*, 10283–10286.
4. (a) Hercouet, A.; Le Corre, M. *Tetrahedron Lett.* **1979**, *23*, 2145–2148; (b) Begasse, B.; Hercouet, A.; Le Corre, M. *Tetrahedron Lett.* **1979**, *23*, 2149–2150; (c) Hercouet, A.; Le Corre, M. *Tetrahedron* **1981**, *37*, 2867–2873.
5. (a) Twyman, L. J.; Allsop, D. *Tetrahedron Lett.* **1999**, *40*, 9383–9384; (b) Capuano, L.; Ahlhelm, A.; Hartmann, H. *Chem. Ber.* **1986**, *119*, 2069–2074; (c) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721; (d) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Soest, R. V.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321–324; (e) De Luca, L.; Giacomelli, G.; Nieddu, G. *J. Org. Chem.* **2007**, *72*, 3955–3957; (f) Guillaumel, J.; Royer, R. *J. Heterocycl. Chem.* **1986**, *23*, 1277–1282; (g) Mali, R. S.; Massey, A. P. *J. Chem. Res. (S)* **1998**, 230–231; (h) Guillaumel, J.; Boccara, N.; Demerseman, P. *J. Heterocycl. Chem.* **1990**, *27*, 1047–1051; (i) Wendt, B.; Ha, H. R.; Hesse, M. *Helv. Chim. Acta* **2002**, *85*, 2990–3001.
6. (a) Bohmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200–3205; (b) Weng, X.; Ren, L.; Weng, L.; Huang, J.; Zhu, S.; Zhou, X.; Weng, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8020–8023; (c) Yanagi, T.; Kikuchi, K.; Takeuchi, H.; Ishikawa, T.; Nishimura, T.; Yamamoto, I. *Chem. Pharm. Bull.* **2001**, *49*, 1018–1023; (d) Sinhababu, A. K.; Borchardt, R. T. *Synth. Commun.* **1983**, *13*, 677–683.
7. *Compound* **11**: To a solution of **3** (1.85 g, 4 mmol) in $CHCl_3$ (20 mL) under nitrogen atmosphere, 4-benzyloxy-3-methoxy benzoyl chloride **10** (1.66 g, 6 mmol) and pyridine (0.65 mL, 8 mmol) were added with stirring. The mixture was refluxed for 2 h. After cooling to rt, Et_3N (2.2 mL, 16 mmol) was added and the mixture was refluxed again for 6 h. The reaction mixture was cooled to rt and extracted with EtOAc (2 × 30 mL), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica gel using ethyl acetate/petroleum ether (3:5) as eluent to give **11** (1.38 g, 89%). White solid; mp 151–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.92 (s, 1H), 7.61 (d, 1H, J = 1.5 Hz), 7.19–7.39 (m, 8H), 6.87–6.89 (m, 2H), 5.14 (s, 2H), 4.01 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.6, 157.9, 150.0, 149.4, 147.5, 145.9, 136.8, 133.5, 131.1, 128.6, 128.0, 127.4, 123.1, 118.8, 118.4, 114.2, 109.0, 104.6, 100.7, 71.1, 56.3, 56.2. IR (KBr): 2925, 2856, 1725, 1688, 1608, 1514, 1274, 1213, 1140, 809, 742, 690 cm^{-1}. HRMS m/z calcd for $C_{24}H_{21}O_5$ $(M+H)^+$ 389.1389, found 389.1386.
8. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
9. (a) Gagey, N.; Neveu, P.; Benbrahim, C.; Goetz, B.; Aujard, I.; Baudin, J.-B.; Jullien, L. *J. Am. Chem. Soc.* **2007**, *129*, 9986–9998; (b) DeZutter, C. B.; Horner, J. H.; Newcomb, M. *J. Phys. Chem. A* **2008**, *112*, 1891–1896.
10. *Compound* **12**: To a solution of **11** (1.01 g, 2.6 mmol) in CH_2Cl_2 (50 mL), under nitrogen atmosphere, (carbethoxymethylene)triphenyl phosphorane, **2** (1.08 g, 3.1 mmol) was added at 0 °C and stirred for 3 h at the same temperature. The contents were brought to rt and stirred for 10 h. The mixture was extracted with CH_2Cl_2, washed with brine, dried and evaporated. The crude product was subjected to column chromatography on silica gel using ethyl acetate/petroleum ether (2:5) as eluent to give **12** (1.18 g, 99%). White solid; mp 142–144 °C (lit.[2d] 142–144 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, 1H, J = 15.9 Hz), 7.18–7.39 (m, 8H), 6.80–6.88 (m, 3H), 6.33 (d, 1H, J = 15.9 Hz), 5.13 (s, 2H), 4.21 (q, 2H, J = 7.2 Hz), 3.98 (s, 3H), 3.91 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 157.2, 149.8, 149.0, 145.4, 145.4, 145.2, 136.8, 131.4, 130.6, 128.7, 128.0, 127.3, 123.4, 118.2, 117.0, 114.6, 113.9, 108.7, 105.2, 100.5, 71.0, 60.5, 56.2, 56.1, 14.4. IR (KBr): 1677, 1598, 1515, 1274, 1231, 1185, 997, 697 cm^{-1}. HRMS m/z calcd for $C_{28}H_{27}O_6$ $(M+H)^+$ 459.1808, found 459.1807.
11. *Compound* **13**: To a stirred solution of **12** (1.10 g, 2.4 mmol) in CH_2Cl_2 (25 mL), under nitrogen atmosphere, $TiCl_4$ (0.30 mL, 2.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred for 5 h at rt. After cooling, the reaction was quenched with methanol and the solvent was evaporated under reduced pressure. The crude product was chromatographed on silica gel using ethyl acetate/petroleum ether (3:5) as eluent to give **13** (804 mg, 91%). White solid; mp 149–150 °C (lit.[2d] 149–151 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, 1H, J = 15.8 Hz), 7.19–7.34 (m, 3H), 6.78–6.92 (m, 3H), 6.34 (d, 1H, J = 16.1 Hz), 5.76 (br s, 1H), 4.21 (q, 2H, J = 7.1 Hz), 3.99 (s, 3H), 3.92 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 157.4, 146.8, 146.7, 145.5, 145.4, 145.2, 131.5, 130.6, 122.5, 119.1, 117.0, 114.9, 114.6, 107.7, 105.1, 100.2, 60.6, 56.2, 56.1, 14.5. IR (KBr): 3400, 2944, 2849, 1711, 1637, 1611, 1594, 1510, 1488, 1278, 1171, 1126, 860, 849 cm^{-1}. HRMS m/z calcd for $C_{21}H_{21}O_6$ $(M+H)^+$ 369.1338, found 369.1335.
12. *Synthesis of ailanthoidol* (**1**): To a solution of $LiAlH_4$ (247 mg, 6.52 mmol) in THF (15 mL), under nitrogen atmosphere, aluminium trichloride (289 mg, 2.17 mmol) was added portionwise. The mixture was stirred for 10 min at rt. Compound **13** (800 mg, 2.17 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 4 h at rt. After completion, the reaction was quenched with ice water, extracted with EtOAc, washed with brine and dried over $MgSO_4$. The crude product was subjected to column chromatography on silica gel using ethyl acetate/petroleum ether (3:5) as eluent to give ailanthoidol **1** (538 mg, 76%). White solid; mp 199–201 °C (lit.[2d] 199–201 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.42 (s, 1H), 7.34 (d, 1H, J = 1.9 Hz), 7.28 (dd, 1H, J = 1.9, 8.0 Hz) 7.24–7.34 (m, 2H), 7.13 (d, 2H, J = 5.0 Hz), 6.96 (d, 1H, J = 1.2 Hz), 6.84 (d, 1H, J = 8.1 Hz), 6.57 (d, 1H, J = 15.7 Hz), 6.34 (dt, 1H, J = 15.7 Hz), 4.83 (t, 1H, J = 5.4 Hz), 4.10 (t, 2H, J = 4.6 Hz), 3.94 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6 125 MHz) δ 155.7, 146.8, 146.5, 143.8, 142.1, 132.3, 130.2, 129.1, 127.8, 120.8, 117.4, 114.8, 110.3, 107.4, 103.3, 98.8, 61.4, 55.0, 55.0. IR (KBr): 3332, 2924, 2853, 1656, 1602, 1514, 1443, 1278, 1211, 1150, 1128, 967 cm^{-1}. HRMS m/z calcd for $C_{19}H_{19}O_5$ $(M+H)^+$ 327.1232, found 327.1234.