Total Synthesis

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Total Synthesis of Linoxepin through a Palladium-Catalyzed Domino Reaction**

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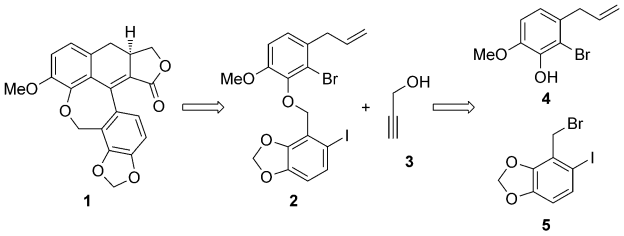
Dedicated to Professor Wolfgang A. Herrmann on the occasion of his 65th birthday

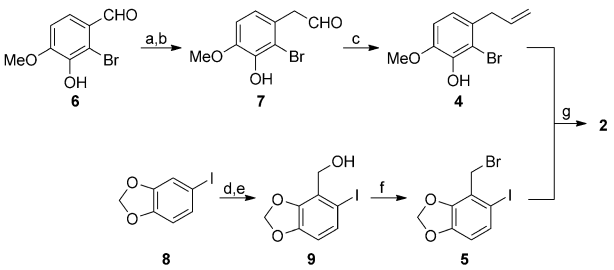
The natural product linoxepin (**1**) belongs to the aryldihydronaphthalene lignans and contains a for this class of compounds so far unprecedented benzonaphtho[1,8-*bc*]oxepine moiety. It was first isolated by Schmidt et al. in 2007 from *Linum perenne* L. (Linaceae), and its absolute configuration was determined by CD spectroscopy in combination with DFT calculations.[1] To date neither a synthetic approach nor any biological studies have been reported. Owing to its close structural resemblance to lignans showing interesting biological profiles (such as podophyllotoxin and the clinically used anticancer agents etoposide and teniposide), the novel lignan is an attractive synthetic goal. To meet the requirements of modern synthetic chemistry and fulfill the demand for an ecologically and economically advantageous approach we developed a novel Pd-catalyzed domino process[2] for its synthesis, which is also suitable for the preparation of analogues. Herein we describe the first total synthesis of (+)- and (−)-linoxepin (**1**) in only ten steps and an overall yield of 30% without the use of any protecting groups.

The retrosynthetic analysis of **1**, based on a threefold Pd-catalyzed domino process that consists of a Sonogashira reaction, a carbopalladation,[3] and a Heck-type reaction, leads to substrates **2** and **3**, where **2** is accessible from phenol **4** and benzylbromide **5** (Scheme 1).

The synthesis of **4** was accomplished in three steps from the aldehyde **6** (Scheme 2).[4] Wittig reaction of **6** using



Scheme 1. Retrosynthetic analysis of linoxepin (**1**).



Scheme 2. a) $MeOCH_2PPh_3Cl$, KO*t*Bu, THF, 0°C→RT, 75 min, 97%; b) 10% HCl (aq.), THF, 70°C, 30 min, 82%, c) H_3CPPh_3Br, KO*t*Bu, THF, 0°C, 75 min, 94%; d) lithium diisopropylamide (LDA), THF, −78°C, 30 min, then DMF, −78°C, 14 h; e) $NaBH_4$, EtOH, 0°C→RT, 1 h, 84% over 2 steps; f) PBr_3, CH_2Cl_2, RT, 18 h, 89%; g) K_2CO_3, MeCN, 80°C, 1 h, 91%.

$MeOCH_2PPh_3Cl$ and subsequent hydrolysis of the formed methyl enol ether afforded aldehyde **7**, which was transformed into alkene **4** by another Wittig transformation in an overall yield of 75%.[5] Benzyl alcohol **9** was prepared from **8**[6] by formylation and subsequent reduction.[7] Reaction of **9** with phosphorus tribromide led to benzyl bromide **5** in an overall yield of 75%. Coupling of **4** and **5** under basic conditions afforded the domino precursor **2** in 91% yield.[8]

Treatment of **2** and **3** with $[Pd(PPh_3)_4]$ as catalyst and TBAF·3 H_2O as base at 80°C in DME allowed us to perform the envisioned domino Sonogashira/carbopalladation/Heck reaction with 50% yield, but the final product was not the expected compound **10** but the aromatic system **11**, which is probably formed from **10** under the employed reaction conditions (Scheme 3).

The synthetic strategy was therefore adjusted by including a silyl-terminated Heck reaction[9] as the last step of the domino process employing an allysilane moiety to allow a controlled elimination of a formal "PdSi" species. In this

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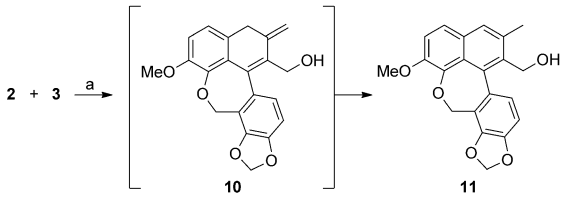


Scheme 3. Domino Sonogashira/carbopalladation/Heck reaction: a) $[Pd(PPh_3)_4]$, tetrabutylammonium fluoride (TBAF)·3 H_2O, 1,2-dimethoxyethane (DME), 80 °C, 24 h, 50%.

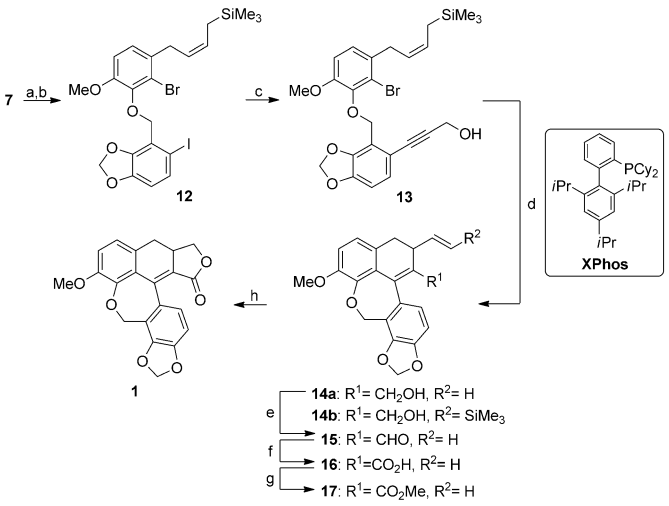
way a vinyl substituent, instead of the *exo*-methylene group as in **10**, would be formed, which should not undergo an isomerization to give the corresponding undesired aromatic system. The substrate for the Pd-catalyzed reaction is again easily accessible (Scheme 4). Wittig reaction of aldehyde **7** with methyltriphenylphosphonium bromide and (iodomethyl)trimethylsilane afforded the allylsilane in 68% yield. Alkylation with benzyl bromide **5** gave benzyl aryl ether **12**. Here we preferred to perform the Sonogashira reaction separately, which is more reliable and gives better yields than its inclusion into a threefold domino process. This is mainly due to the fact that CuI cannot be used in the domino process, since it inhibits the carbopalladation and the Heck reaction. Treatment of **12** with propargyl alcohol (**3**) in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ and CuI as well as Bu_4NOAc as base at 60 °C for 30 min provided alkyne **13** in 98% yield.

In the following domino carbopalladation/Heck reaction best results were obtained by using $Pd(OAc)_2$ with XPhos as ligand and Bu_4NOAc as base in DME at 80 °C to afford the desired terminal alkene **14a** in 76% yield; in addition 13% of the vinylsilane **14b** was isolated. We used several other achiral and also chiral ligands, such as BINAP and KenPhos,[10] as well as different Pd sources. In all these cases the yields of the desired compound **14a** were lower. Moreover, when using the chiral ligands an enantioselective reaction was not observed. A final explanation for this result cannot be given yet.

For the completion of the total synthesis of linoxepin (**1**), the alcohol **14a** was oxidized in a two-step procedure using the Dess–Martin periodinane and subsequently the Pinnick oxidation to give the corresponding acid, which was transformed into the methyl ester **17** by means of trimethylsilyldiazomethane in 91% yield over three steps. Controlled ozonolysis in the presence of the dye solvent red 19 allowed a selective cleavage of the vinyl group,[11] and finally reductive work-up of the reaction mixture directly afforded racemic linoxepin (**1**) in 80% yield.

To prepare the two enantiomers (+)-(*R*)- and (−)-(*S*)-linoxepin, the racemic alcohol **14a** was resolved by chromatography on chiral support using an IA column. The following steps were identical with those used in the synthesis of the racemic compound. The spectroscopic data of the final products are in good agreement with those published by Schmidt et al.[1] except the optical rotation, which with $[\alpha]_D^{22} = +96.1$ is higher than the published value with $[\alpha]_D^{20} = +23$. In contrast, the CD spectrum of the synthetic (+)-linoxepin (**1**) corresponds very well with that of the natural material.

To confirm the proposed absolute configuration of the natural (+)-linoxepin (**1**) we analyzed crystals of the unnatural (−)-linoxepin (*ent*-**1**), which gave crystals of higher quality. Owing to the lack of a heavy atom, the dataset was collected using the K_α radiation of a copper rotating anode. The single-crystal X-ray diffraction analysis showed that (−)-linoxepin (*ent*-**1**) has the *S* configuration, thereby proving the *R* configuration for the natural product (Figure 1).[12,13]



Scheme 4. Synthesis of linoxepin (**1**): a) Ph_3PCH_3Br, KO*t*Bu, ICH_2SiMe_3, THF, 0 °C, 3 days, 68%; b) **5**, K_2CO_3, MeCN, 80 °C, 5 h, 99%; c) **3**, $[Pd(PPh_3)_4]$ (7 mol%), CuI (10 mol%), Bu_4NOAc, dioxane, 60 °C, 30 min, 98%; d) $Pd(OAc)_2$ (5 mol%), XPhos (7.5 mol%), Bu_4NOAc, DME, 80 °C, 1 h, 76% **14a** and 13% **14b**; e) Dess–Martin periodinane, CH_2Cl_2, RT, 2 h, 92%; f) $NaClO_2$, $NaH_2PO_4·H_2O$ in H_2O, 2-methyl-2-butene, *t*BuOH/THF 4:1, RT, 2 days, 99%; g) $TMSCHN_2$ (2 M in Et_2O), benzene/MeOH 10:1, 0 °C, 15 min, quant.; h) O_3, solvent red 19 (0.05% in EtOH), EtOH, −78 °C, then $NaBH_4$, −78 °C→RT, 16 h, 80%.

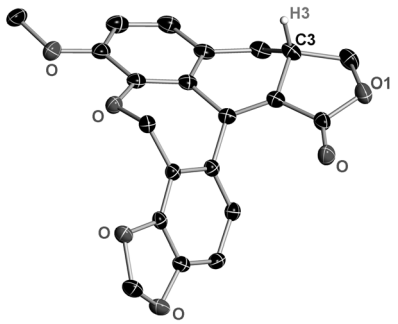


Figure 1. Crystal structure of (−)-(*S*)-linoxepin (*ent*-**1**). (Flack x parameter: −0.05(8)).[14] The hydrogen atoms apart from H3 are omitted for clarity, and the anisotropic displacement parameters are depicted at the 50% probability level.

In conclusion we have developed a highly elegant and very robust synthesis, which includes multiple Pd-catalyzed reactions, of the lignan linoxepin (**1**) by using a Sonogashira reaction and a domino carbopalladation/Heck reaction of an allylsilane. This synthesis offers a high degree of versatility in

respect to aromatic substitution patterns and functional group tolerance to also prepare analogues.

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Experimental Section

(11-Methoxy-7-vinyl-8,13-dihydro-7*H*-[1,3]dioxolo[4′,5′:3,4]benzo-[1,2-*e*]naphtho[1,8-*bc*]oxepin-6-yl)methanol (**14a**): An oven-dried flask was charged with alkyne **13** (1.00 g, 1.93 mmol, 1.00 equiv), $Pd(OAc)_2$ (21.7 mg, 96.5 μmol, 5.00 mol%), XPhos (69.1 mg, 145 μmol, 7.50 mol%), and tetrabutylammonium acetate (1.16 g, 3.86 mmol, 2.00 equiv). DME (20 mL) was added and the mixture was heated to 80 °C for 1.5 h (preheated oil bath). The reaction mixture was diluted with CH_2Cl_2 (30 mL), silica gel was added, and the solvent was removed in vacuo. Column chromatography (SiO_2, PE/EA = 4:1→3:1) yielded the desired product (535 mg, 1.47 mmol, 76%) as a colorless foam in approximately 95% purity. In addition the vinyl silane **14b** (112 mg, 0.257 mmol, 13%) was isolated as by-product. $R_f = 0.23$ (PE/EA = 2:1). UV(CH_3CN): λ_{max} (lg ε) = 200.0 nm (4.598), 286.0 (4.041). IR (neat): $\tilde{\nu}$ =3287, 2911, 1462, 1432, 1258, 1232, 1214, 1099, 1029, 1011 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.73$ (dd, J = 14.9, 1.7 Hz, 1H, 8′-H_A), 3.01 (ddd, J = 14.9, 5.7, 0.8 Hz, 1H, 8′-H_B), 3.30 (t, J = 5.7 Hz, 1H, 7′-H), 3.79 (s, 3H, OCH_3), 4.16 (q, J = 11.8 Hz, 2H, 1′-H_2), 4.91 (ddd, J = 10.1, 1.6, 0.9 Hz, 1H, 2″-H_A), 5.09 (d, J = 12.3 Hz, 1H, 13-H_A), 5.06–5.16 (m, 1H, 2″-H_B), 5.23–5.34 (m, 1H, OH), 5.31 (d, J = 12.3 Hz, 1H, 13-H_B), 5.74 (ddd, J = 17.3, 10.1, 7.4 Hz, 1H, 1″-H), 5.98 (dd, J = 10.5, 1.4 Hz, 2H, 2′-H_2), 6.65 (d, J = 8.1 Hz, 1H, 10′-H), 6.68–6.73 (m, 2H, 9′-H, 4′-H), 6.76 ppm (d, J = 7.9 Hz, 1H, 5′-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 35.5$ (C-8′), 39.8 (C-7′), 56.0 (OCH_3), 62.7 (C-1), 64.2 (C-13′), 101.5 (C-2′), 107.7 (C-4′), 109.7 (C-10′), 115.2 (C-2″), 117.7 (C-13a′), 119.9 (C-9′), 121.8 (C-5b$^{1\prime}$), 122.6 (C-5′), 128.0 (C-8a′), 133.2 (C-5a′), 133.6 (C-5b′), 137.3 (C-1″), 139.6 (C-6), 144.7 (C-13b′), 146.0 (C-11a′), 147.4 (C-3a′), 148.6 ppm (C-11′). MS (ESI): m/z (%) = 387.1 (64) $[M+Na]^+$, 751.3 (100) $[2M+Na]^+$, 1115.4 (86) $[3M+Na]^+$. HRMS (ESI): m/z calc. for $C_{22}H_{20}O_5$: 387.1203, found: 387.1203, $[M+Na]^+$.

Linoxepin (**1**): Ester **17** (39 mg, 0.10 mmol, 1.0 equiv) was dissolved in EtOH (10 mL) (ultrasonic bath), a solution of solvent red 19 (0.05% in EtOH, 0.60 mL) was added and the red solution was cooled to −78 °C. O_3 was bubbled through the solution until the red color vanished. Then Ar was bubbled through the solution to remove excess O_3. Sodium borohydride (15 mg, 0.40 mmol, 4.0 equiv) was added and the mixture was allowed to warm to RT overnight. The solution was separated from the yellow residue, poured into sat. aq. NH_4Cl sol. (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The yellow residue was dissolved in CH_2Cl_2 (10 mL), the organic phases were combined and dried over $MgSO_4$. After removal of the solvent in vacuo, column chromatography (SiO_2, CH_2Cl_2) afforded the desired product (29 mg, 0.08 mmol, 80%) as a yellow solid. R_f = 0.21 (PE/EA = 2:1). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.64$ (dt, J = 14.9, 1.1 Hz, 1H, 9-H_A), 2.98 (dd, J = 14.6, 5.7 Hz, 1H, 9-H_B), 3.26 (ddt, J = 14.6, 8.8, 5.7 Hz, 1H, 9a-H), 3.83 (s, 3H, OCH_3), 4.01 (t, J = 8.7 Hz, 1H, 10-H_A), 4.66 (t, J = 8.9 Hz, 1H, 10-H_B), 5.12 (d, J = 12.5 Hz, 1H, 4-H_A), 5.37 (d, J = 12.5 Hz, 1H, 4-H_B), 6.01 (d, J = 1.9 Hz, 1H, 2-H_A), 6.01 (d, J = 1.9 Hz, 1H, 2-H_B), 6.72 (d, J = 8.0 Hz, 1H, 14-H), 6.78 (d, J = 8.2 Hz, 1H, 7-H), 6.83 (d, J = 8.2 Hz, 1H, 8-H), 6.85 ppm (d, J = 8.0 Hz, 1H, 13-H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 34.5$ (C-9), 36.9 (C-9a), 56.2 (OCH_3), 64.7 (C-4), 70.0 (C-10), 101.8 (C-2), 108.1 (C-14), 111.8 (C-7), 116.5 (C-3b), 119.8 (C-8), 122.2 (C-5a^1), 124.1 (C-13), 124.3 (C-12a), 128.1 (C-8a), 129.4 (C-12c), 144.7 (C-3a), 145.6 (C-12b), 148.5 (C-5a), 149.0 (C-14a), 149.4 (C-6), 168.7 ppm (C-12). MS (ESI): m/z (%) = 365.1 (46) $[M+H]^+$, 387.1 (98) $[M+Na]^+$, 751.2 (100) $[2M+Na]^+$, 1115.3 (17) $[3M+Na]^+$. HRMS (ESI): m/z calc. for $C_{21}H_{16}O_6$: 365.1020, found: 365.1019, $[M+H]^+$.

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