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Domino Wittig–Diels Alder reaction: synthesis of carbazole lignans

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ABSTRACT

A convenient two step protocol for the synthesis of carbazole lignans involving Domino Wittig reaction/Diels Alder reaction followed by aromatization with DDQ is described. The main step of this protocol involves interaction between 2- or 3-indolecarboxyaldehydes and cinnamyl 2-(triphenylphosphoranylidene)acetates.

Furanone moiety fused to a cyclic framework is a structural feature found in many biologically active compounds.[1] For example podophyllotoxin (**1a**) a naturally occurring lignan is a drug used in the treatment of cancer.[2] Taiwanin C (**2a**) and justicidin E (**2b**) are two naturally occurring naphthalene lignans where furanone ring is fused with the aromatic ring.[3] When one of the aromatic rings in the lignan skeleton is replaced by a heterocycle it is usually termed as heterolignan. Azatoxin (**3a**) and 8′-azapodophyllotoxin (**1b**) are two successfully designed and synthesized potent azaligнans. Isoelliptitoxin (**3b**) is an indole analogue of deoxypodophyllotoxin (Fig. 1).[4] Heterolignans are of interest due to their potential biological activities and efforts are ongoing to synthesize them.[5] In continuation of our interest in Domino Wittig–Diels Alder reaction sequence,[6] we report herein synthesis of a series of indole lignans.

Thus, when indole-2-carboxyaldehyde **4** was subjected to Domino Wittig–Diels Alder reaction protocol with phosphorane **6a**, a mixture of two diastereomers **8a** and **8b** was obtained in 9:1 ratio in 63% yield (Scheme 1).[7] The major isomer **8a** was obtained as a white solid while the minor was a viscous oil. We could not unambiguously decide the nature of the geometry of the two isomers based on their NMR data. Recourse was taken to single crystal X-ray diffraction analysis in the case of solid **8a** which afforded suitable crystals for structure determination (Fig. 2).[8]

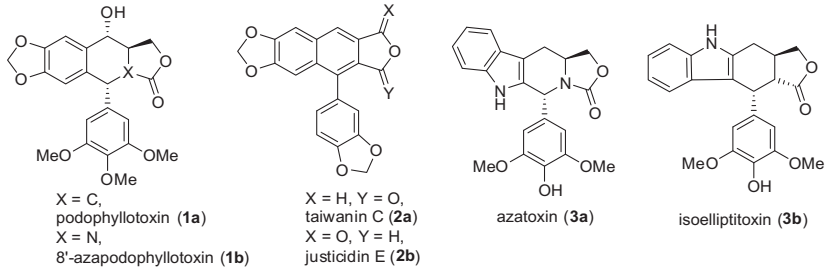

Figure 1. Structures of some naturally occurring lignans.

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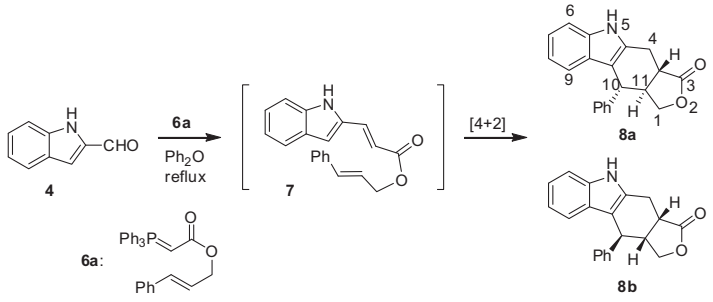


Scheme 1. Domino Wittig reaction Diels–Alder reaction protocol.

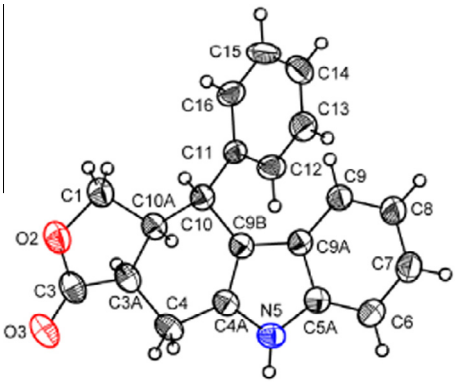


Figure 2. Crystal structure for **8a**. Displacement ellipsoids have been drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

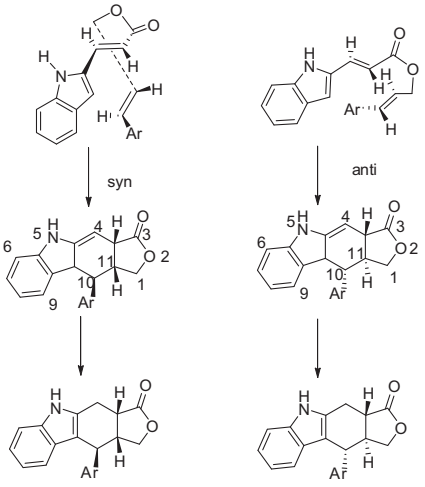
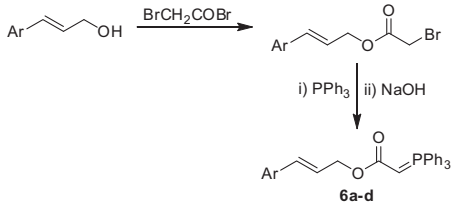


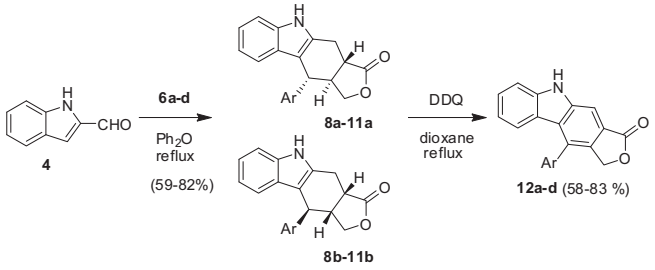
Figure 3. Transition state involved in Diels–Alder reaction.

In this one pot sequence first the Wittig reaction takes place to form the (*E*)-unsaturated ester **7**, which undergoes [4+2] cycloaddition either in *syn* or *anti* mode (Fig. 3) followed by rapid isomerization to give a mixture of **8a** and **8b**. The formation of both the diastereoisomers in unequal proportion suggests that the energy barrier between the two transition states is different and favors the *anti* transition state. It was observed that the diastereoisomer in which the six and five membered rings are *trans* fused to each other was formed in more proportion than the *cis* fused one, as indicated by the orientation of the protons attached at C10A and C3A (Fig. 2).

Having successfully synthesized the tetrahydrocarbazole lignan skeleton **8**, the synthesis of its analogues **9**–**11** was undertaken. The required phosphoranes **6b**–**d** were prepared from the corresponding cinnamyl alcohols (Scheme 2). These phosphoranes were then condensed with **4** to obtain **9**–**11** (Scheme 3) in moderate to good yields. The tetrahydrocarbazole lactones were then aromatized using DDQ to carbazole lignans **12a**–**d** in good yields (Table 1). A one pot procedure was attempted for the direct preparation of **12a** by refluxing a mixture of **4**, **6a** and 10% Pd—C in diphenyl ether. However the product **12a** was obtained in mere 32% yield. Hence the two-step protocol was preferred.



Scheme 2. Synthesis of phosphoranes **6a**–**d** from cinnamyl alcohols.

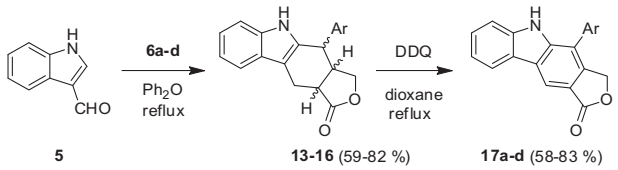


Scheme 3. Synthesis of lignans **12a**–**d**.

Table 1
Tetrahydrocarbazole (**8**–**11**; **13**–**16**) – carbazole (**12**, **17**) lignans

Entry	Products	Ratio (**a**/**b**)	Total yield (%)	DDQ aromatized product	Yield (%)
1	**8a**/**8b**	9/1[a]	63	**12a**	60
2	**9a**/**9b**	10/1[b]	75	**12b**	78
3	**10a**/**10b**	Traces of **b**	82	**12c**	83
4	**11a**/**11b**	7/3[a]	59	**12d**	58
5	**13a**/**13b**	Traces of **b**	62	**17a**	61
6	**14a**/**14b**	Traces of **b**	60	**17b**	60
7	**15a**/**15b**	Traces of **b**	76	**17c**	79
8	**16a**/**16b**	Traces of **b**	56	**17d**	56

[a] Isolated ratio.
[b] Ratio based on ^{1}H NMR.



Scheme 4. Synthesis of lignans **17a–d**.

After successfully synthesizing the carbazole lignans **12a–d**, the two-step protocol was evaluated for the synthesis of isomeric carbazole lignans **17a–d**. Thus indole-3-carboxyaldehyde **5** was condensed with the phosphoranes **6a–d** to obtain tetrahydrocarbazoles **13–16**, which were then oxidized with DDQ to provide the carbazole lignans **17a–d** (Scheme 4, Table 1).

In conclusion, we have demonstrated that isomeric carbazole lignans can be conveniently assembled by Domino Wittig–Diels Alder reaction sequence followed by aromatization with DDQ.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data, copies of ^{1}H, ^{13}C NMR spectra and structure protocol of **8a**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.038.

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7. *General procedure for the preparation of substituted cinnamyl phosphoranes* **6a–d**: A solution of substituted cinnamyl alcohol (1 mmol) and pyridine (1 mmol) in dry chloroform (20 mL) was cooled to 0 °C. Bromoacetyl bromide (1 mmol) was added dropwise with stirring over a period of 15 min. The mixture was stirred for 1 h at 0 °C and further at room temperature for 1 h. To the reaction mixture, water (20 mL) was added and extracted with chloroform (2 × 25 mL). The organic layer was washed with 2 N HCl (2 × 15 mL), satd sodium bicarbonate (2 × 20 mL) and finally with water (20 mL). The chloroform layer was dried over anhyd sodium sulfate. Evaporation of the solvent under vacuum gave crude cinnamyl 2-bromoacetate which was as such used for the next reaction. The solution of cinnamyl 2-bromoacetate (1 mmol) and triphenylphosphine (1.05 mmol) in dry toluene (20 mL) was stirred overnight at room temperature. The salt formed was filtered and dissolved in methanol (5 mL). To this water (20 mL) and toluene (40 mL) was added, followed by addition of 2 N sodium hydroxide solution with stirring to phenolphthalein end point. The toluene layer was separated and the aqueous layer was extracted with toluene (2 × 20 mL). The toluene layer was dried over anhyd. sodium sulfate and the solvent removed under vacuum to give substituted cinnamyl (triphenylphosphoranylidene)acetate.
General procedure for the preparation of tricyclic γ-lactones **8–11** *and* **13–16**: A solution of indolecarboxaldehyde (1 mmol) and phosphorane **6a–d** (1.5 mmol) in diphenyl ether (10 mL) was refluxed for 1–2 h. The crude mixture was subjected to column chromatography over silica gel using hexanes to remove diphenyl ether first and further elution with 30–50% ethyl acetate in hexanes to afford diastereomeric γ-lactones.
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General procedure for the preparation of indole based heterolignans **12a–d** *and* **17a–d**:
A mixture of tetrahydrolignans (1 mmol) and DDQ (2.5 mmol) in dioxane (10 mL) was refluxed for 2 h. The reaction mixture was allowed to cool to ambient temperature and filtered. The filtrate was then concentrated under reduced pressure and resulting residue was dissolved in ethyl acetate (50 mL) and washed with satd sodium bicarbonate (2 × 10 mL) and water (2 × 10 mL). The organic layer was dried over anhyd sodium sulfate and concentrated under reduced pressure. The resulting residue on purification using flash chromatography with hexanes/ethyl acetate gave the oxidized products.
8. Crystal data for **8a**: $C_{20}H_{17}NO_2$, $M = 303.35$, monoclinic, space group $P2_1/c$, $a = 12.879(3)$ Å, $b = 6.2881(14)$ Å, $c = 19.076(4)$ Å, $\beta = 93.163(4)°$, $V = 1542.5(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.306$ Mg/m^3, $F(000) = 640$, $\mu = 0.084$ mm^{-1}, $R = 0.0417$, $wR = 0.1141$, GOF = 1.050 for 2717 reflections with $I > 2\sigma(I)$. www.ccdc.cam.ac.uk/conts/retrieving.html Crystallographic data (excluding structure factors) for the structure of **8a** reported herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1453376. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK. (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).