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The First Direct Synthesis of Pterocarpans *via* Aldol Condensation of Phenylacetates with Benzaldehydes

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Abstract: Aldol condensation between phenylacetates and benzaldehydes affords 2,3-diaryl-3-hydroxypropanoates which are converted into pterocarpans in moderate to high yields.

Apart from the isoflavones, pterocarpans represent the second largest group of natural isoflavonoids, with medicarpin and maackiain occurring almost ubiquitously.[1] Among the variety of synthetic routes to pterocarpans, the most common approach involves the cumbersome process of reduction and cyclization of the corresponding 2'-hydroxy-isoflavanones.[2] In addition, Heck arylation[3,4] and 1,4-benzoquinone cycloaddition[5,6] of chromenes have been utilized to obtain pterocarpans, while a 1,3-Michael-Claisen annulation reaction[7,8] forming an aromatic ring has also been exploited. The utility of these routes is, however, limited by their inability to address the issue of stereocontrol at C-6a and C-11a, which is a prerequisite for the formation of the naturally occurring compounds. Owing to the demand for enantiomerically pure pterocarpans a more direct synthetic approach that is based on the aldol condensation between appropriately protected phenylacetates and benzaldehydes, and which possesses the potential of introducing stereoselectivity, was thus developed.

Consideration of the simple *retro*-synthetic sequence, **1** ⇒ **2** ⇒ **3** ⇒ **4** + **5**, indicates that our protocol for constructing the C_6-C_3-C_6 framework would involve the synthesis of oxygenated phenylacetates **5** (C_6-C_2 fragment involving the D-ring) and benzaldehydes **4** (C_6-C_1 fragment involving the A-ring), aldol condensation between **4** and **5** to give 2,3-diaryl-3-hydroxypropanoates of type **3**, and subsequent reduction and consecutive cyclizations to give the pterocarpans, e.g. **1** (Scheme 1).

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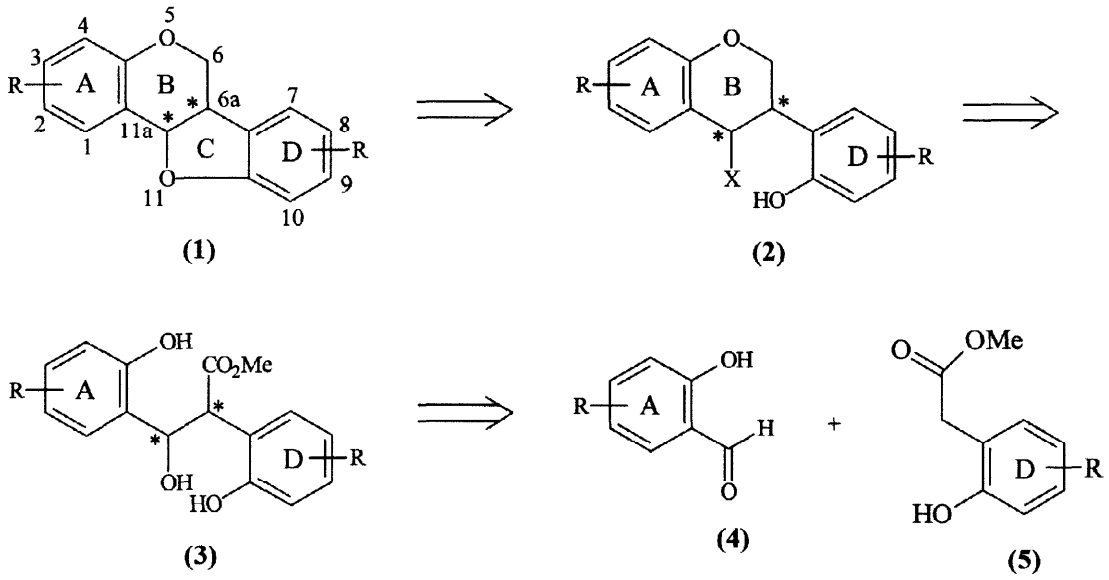
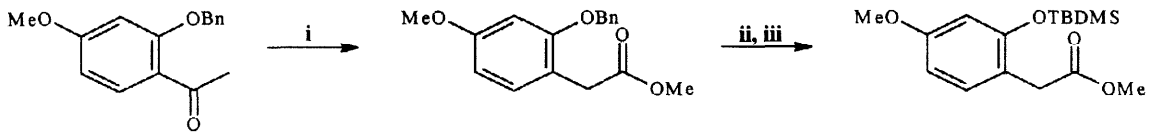


R = H, OMe; X = leaving group

Scheme 1

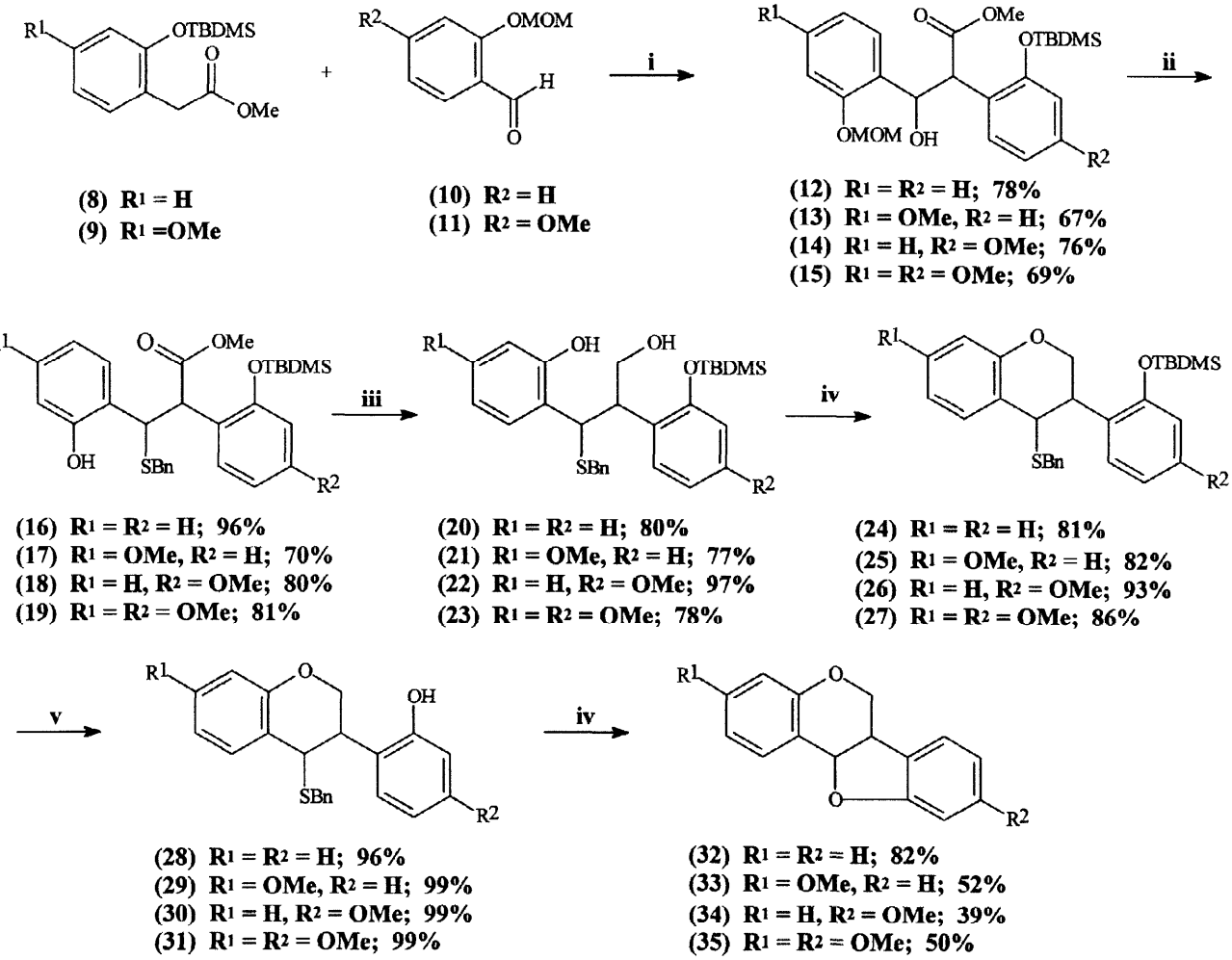
Since the B-ring of the pterocarpan backbone had to be constructed first, protecting groups for the 2-hydroxyl functions in **4** and **5** had to be carefully selected. Thus, the benzaldehydes **10** and **11** were protected by a methoxymethyl (MOM) group,[9] which is labile in the presence of Lewis acids such as tin tetrachloride ($SnCl_4$).[10] A silyl ether was then selected as phenol protective group in the preparation of the phenylacetates **8** and **9**, because of its stability[11] towards Lewis acids and potential for deprotection at a later stage. Owing to the commercial unavailability of 2-hydroxy-4-methoxyphenylacetic acid, the requisite phenylacetate **9** was prepared *via* a thallium(III)nitrate (TTN) oxidative rearrangement[12] of 2-benzyloxy-4-methoxyacetophenone **6**, followed by debenzylation and silylation (Scheme 2).



Scheme 2 *Reagents and conditions*: i) TTN, $HClO_4$, MeOH, rt; ii) H_2/Pt, acetone, rt; iii) TBDMSCl, imidazole, DMF, rt.

The consecutive steps towards formation of the pterocarpans were performed according to the sequence in Scheme 3. Owing to the excellent results reported[13-15] for aldolisation between esters and aldehydes employing

lithium diisopropylamide (LDA), this hindered base was selected for the generation of the *trans*-enolates[15] from esters **8** and **9**. The efficiency of this system to produce the ester enolates within 30 min at -78°C was demonstrated *via* quenching of the reaction with D_2O. The ester enolates were subsequently reacted with the benzaldehydes **10** and **11** to afford the 2,3-diaryl-3-hydroxypropanoates **12-15** in moderate to good yields (67-78%). Next, the Lewis acid, tin tetrachloride ($SnCl_4$), in the presence of the powerful nucleophile, phenylmethanethiol (BnSH), was utilized for cleavage of the C_3-OH bond and subsequent selective removal of the methoxymethyl group to give the 2,3-diaryl-3-benzylsulfanylpropanoates **16-19** in 70-96% yield.[10] These were smoothly converted into the corresponding 3-benzylsulfanylpropanol derivatives **20-23** (77-97% yield) by reduction with lithium aluminium hydride in diethyl ether at room temperature.



(8) R^1 = H
(9) R^1 = OMe

(10) R^2 = H
(11) R^2 = OMe

(12) R^1 = R^2 = H; 78%
(13) R^1 = OMe, R^2 = H; 67%
(14) R^1 = H, R^2 = OMe; 76%
(15) R^1 = R^2 = OMe; 69%

(16) R^1 = R^2 = H; 96%
(17) R^1 = OMe, R^2 = H; 70%
(18) R^1 = H, R^2 = OMe; 80%
(19) R^1 = R^2 = OMe; 81%

(20) R^1 = R^2 = H; 80%
(21) R^1 = OMe, R^2 = H; 77%
(22) R^1 = H, R^2 = OMe; 97%
(23) R^1 = R^2 = OMe; 78%

(24) R^1 = R^2 = H; 81%
(25) R^1 = OMe, R^2 = H; 82%
(26) R^1 = H, R^2 = OMe; 93%
(27) R^1 = R^2 = OMe; 86%

(28) R^1 = R^2 = H; 96%
(29) R^1 = OMe, R^2 = H; 99%
(30) R^1 = H, R^2 = OMe; 99%
(31) R^1 = R^2 = OMe; 99%

(32) R^1 = R^2 = H; 82%
(33) R^1 = OMe, R^2 = H; 52%
(34) R^1 = H, R^2 = OMe; 39%
(35) R^1 = R^2 = OMe; 50%

Scheme 3 *Reagents and conditions*: i) LDA (1.1 eq.), Et_2O, -78°C, then the benzaldehydes, -78 to 0°C; ii) BnSH, $SnCl_4$, CH_2Cl_2, 0°C; iii) $LiAlH_4$, Et_2O, rt; iv) PPh_3, DEAD, rt; v) TBAF(silica), THF, rt; vi) AgOTf or DMTSF. CH_2Cl_2, 0°C.

The isoflavans **24-27** were formed in excellent yields (81-93%) by applying Mitsunobu cyclization conditions[16] (PPh_3-diethyl azodicarboxylate) to compounds **20-23**. Subsequent cleavage of the silyl ethers **24-27** by TBAF on silica[17] in THF at room temperature, and treatment of compounds **28-31** with the thiophilic Lewis acids, dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[18] or silver trifluoromethanesulfonate (CF_3SO_3Ag),[19] gave the pterocarpans **32-35** in yields of 39 and 50-82%, respectively.

We have thus developed a novel synthetic route towards pterocarpans. This protocol should contribute substantially towards the chemistry of the pterocarpans and has the potential to address the stereoselective synthesis of these compounds, a process which is currently being pursued and will be the subject of an impending publication.

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