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A facile synthesis of dihydronaphthopyrans

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Efficient syntheses of naturally occurring linear dihydronaphthopyran **(6a)** and its angular analogues **(3b** and **4)**, from appropriate ortho-methoxynaphthaldehydes, have been described.

Keywords: linear and angular dihydronaphthopyrans, ortho-methoxynaphthaldehydes, Wittig reaction, benzocoumarins

Naphthopyrans constitute the core structure of several biologically active compounds of natural origin. The angular naphthopyran, mollugin[1] (**1**), for example, has been isolated from *Pentas longiflora* while lapachenole[2] (**2**), dihydrolapachenole[3] (**3**) and their 6-demethoxy derivatives[4] (**2a** and **3a**) have been reported from *Tabebuia chrysantha*, *Paratecoma alba* and *Asperula odorata* respectively.

Extensive work regarding the biological activity of naphthopyrans has not been carried out. Nonetheless, their counterparts, the benzopyrans act as non-steroidal antifertility agents[5] and exhibit antijuvenile hormone (AJH) activity[6] and photochromic properties.[7]

Recently we have initiated efforts on the biological screening as well as the convenient synthesis of naphthopyrans and pyranonaphthoquinone antibiotics. A rapid, synthesis of angular and linear 3,4-dihydronaphthopyrans (**3b, 4** and **6a**), having potential herbicidal and fungicidal properties, was therefore required. Several syntheses[8-18] leading to naphthopyrans (**3b, 4** and **6a**) have been reported so far. The linear dihydronaphthopyran (**6a**), isolated by Anjaneyulu *et al.*[19] from the roots of *Withania somnifera*, was first synthesised by Bell and Duewell[9] via the ring closure of 3-(5,6,7,8-tetrahydro-2-naphthyloxy)propionic acid followed by dehydrogenation. Beckwith *et al.*[11] have reported the synthesis of angular naphthopyran (**4**) involving consecutive ring closure and neophyl rearrangement of alkenyl aryl radicals. However, in this case 3-methylnaphthofuran was formed as a by-product. Another route involving photolysis[14] of 3-(2-naphthoxy) propyl-cobaloxime and 3-(1-naphthoxy)propyl-cobaloxime provides the desired angular and linear dihydronaphthopyrans in low yields along with other products. These results promoted us to develop an alternate approach for the synthesis of angular and linear dihydronaphthopyrans (**3b, 4** and **6a**).

Earlier we had reported[20] a convenient method for the synthesis of naturally occurring 2,2-dimethylnaphtho[1,2-*b*]pyrans (**2** and **3**), their dihydro derivatives (**2a** and **3a**) and two novel linear 2,2-dimethylnaphtho[2,3-*b*] pyrans (**5** and **6**) and now we report a simple, inexpensive synthesis of naturally occurring linear 3,4-dihydronaphthopyran (**6a**) and its angular analogues (**3b** and **4**) starting from easily accessible ortho-methoxynaphthaldehydes via the intermediacy of benzocoumarins. The synthetic approach developed (Scheme 1) for linear dihydronaphthopyran (**6a**) involves the use of the Wittig reaction in the key step. Thus, 3-Methoxy-2-naphthaldehyde[21] (**7**) was demethylated by anhydrous $AlCl_3$ in dry dichloromethane to give 3-hydroxy-2-naphthaldehyde[22] (**7a**) in 90% yield. Subsequently, a solution of (**7a**) and (carbethoxymethylene)triphenyl phosphorane in dry xylene was added and the mixture refluxed for 13 hours to obtain the linear benzocoumarin (**10**) in 80% yield. Further, transformation of (**10**) into its dihydro derivative (**11**) was achieved by treating a hot solution of (**10**) in 20% aq. NaOH with Ni–Al alloy. Since the residue obtained after acidic workup of this reaction comprised some uncyclised product, it was subjected to cyclisation in presence of *para*-toluenesulfonic acid (*p*-TSA) and dry benzene using a Dean–Stark separator to furnish 3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-2-one (**11**) in 85% yield. The lactone (**11**) was reduced with lithium aluminium hydride ($LiAlH_4$) in dry ether. In this case too, since the residue obtained after workup comprised some uncyclised product, it was subjected to cyclisation in presence of *p*-TSA and dry benzene using a Dean–Stark separator to afford the desired linear dihydronaphthopyran (**6a**) in 65% yield.

Similarly, the angular dihydronaphthopyrans (**3b**) and (**4**) have also been synthesised (Scheme 1) from 1-methoxy-2-naphthaldehyde (**8**) and 2-methoxy-1-naphthaldehyde (**9**) respectively.

To conclude, we have demonstrated an efficient, practical synthesis of linear as well as angular dihydronaphthopyrans (**3b, 4 and 6a**) from easily accessible starting materials. The present studies also provide a useful general approach for building a dihydronaphthopyran system.

Reagents and conditions

(i) $AlCl_3$–CH_2Cl_2, stir, R.T., 1h; (ii) $Ph_3P{=}CHCOOC_2H_5$, dry xylene, reflux, 13h; (iii) Ni-Al, 20% aq. NaOH, 80–90° C, stir, 1h; (iv) p-TSA, dry benzene, reflux, 1h; (v) $LiAlH_4$, dry Et_2O, stir, R.T., 1h.

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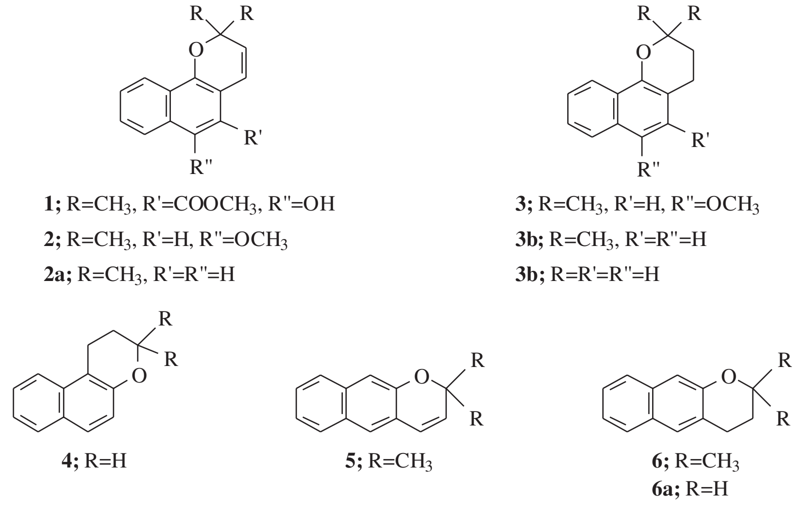


1; R=CH_3, R'=$COOCH_3$, R"=OH

2; R=CH_3, R'=H, R"=OCH_3

2a; R=CH_3, R'=R"=H

3; R=CH_3, R'=H, R"=OCH_3

3b; R=CH_3, R'=R"=H

3b; R=R'=R"=H

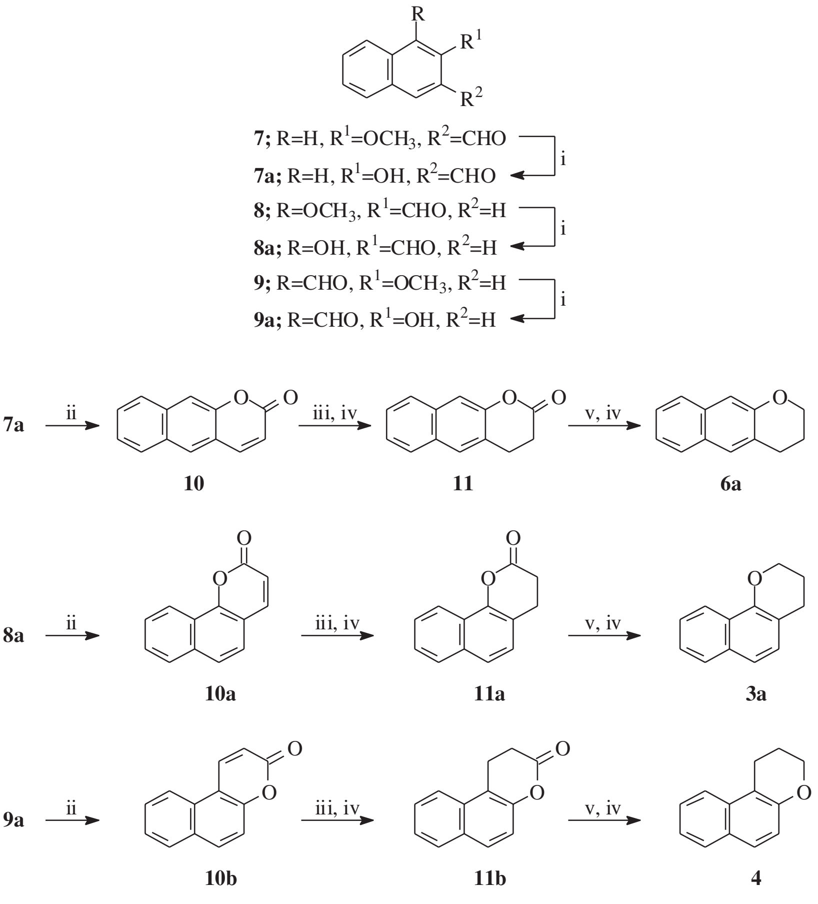
4; R=H

5; R=CH_3

6; R=CH_3

6a; R=H

Fig. 1



7; R=H, R^1=OCH_3, R^2=CHO

7a; R=H, R^1=OH, R^2=CHO

8; R=OCH_3, R^1=CHO, R^2=H

8a; R=OH, R^1=CHO, R^2=H

9; R=CHO, R^1=OCH_3, R^2=H

9a; R=CHO, R^1=OH, R^2=H

Scheme 1

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