A facile synthesis of dihydronaphthopyrans

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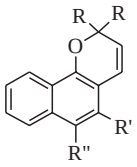
Efficient syntheses of the naturally occurring linear dihydronaphthopyran (**6a**) and its angular analogues (**3b** and **4**), from the appropriate *ortho*-methoxynaphthaldehydes, are described.

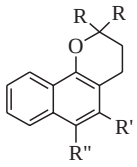
Keywords: dihydronaphthopyrans, *ortho*-methoxynaphthaldehydes, Wittig reactions, benzocoumarins

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

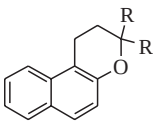
Hitherto, extensive work on the biological activity of naphthopyrans has not been carried out. Nonetheless, their counterparts, the benzopyrans, are known to act as non-steroidal antifertility agents[5] and exhibit antijuvenile hormone (AJH) activity[6] and photochromic properties.[7]



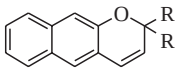
1; R=CH_3, R'=$COOCH_3$, R"=OH
2; R=CH_3, R'=H, R"=OCH_3
2a; R=CH_3, R'=R"=H



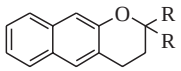
3; R=CH_3, R'=H, R"=OCH_3
3a; R=CH_3, R'=R"=H
3b; R=R'=R"=H



4; R=H



5; R=CH_3



6; R=CH_3
6a; R=H

In recent years we have initiated efforts on the screening for biological activity as well as the development of newer methods for the synthesis of naphthopyrans and pyranonaphthoquinone antibiotics, and in continuation of this ongoing programme rapid, practical and specific syntheses of angular and linear 3,4-dihydronaphthopyrans (**3b, 4** and **6a**), having potential herbicidal and fungicidal properties, are indispensable. Several syntheses[8-18] leading to naphthopyrans (**3b, 4** and **6a**) have been reported so far in the literature. The linear dihydronaphthopyran (**6a**), isolated recently by Anjaneyulu *et al*.[19] from the roots of *Withania somnifera*, was synthesised for the first time 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 the 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 of 3-(2-naphthoxy)propyl cobaloxime and 3-(1-naphthoxy) propyl cobaloxime provides the desired angular and linear dihydronaphthopyrans in low yields along with variety of other products.[14] These results prompted us to devise an alternative approach for the rapid and exclusive synthesis of angular and linear dihydronaphthopyrans (**3b, 4** and **6a**).

Earlier, we published a convenient method for the synthesis of the 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**),[20] and now we report a simple and inexpensive synthesis of the naturally-occurring linear 3,4-dihydronaphthopyran (**6a**) and its angular analogues (**3b** and **4**) starting from easily accessible *ortho*-methoxy-naphthaldehydes via the intermediacy of benzocoumarins.

The synthetic approach developed (Scheme 1) for the linear dihydronaphthopyran (**6a**) involves the Wittig reaction. 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. A solution of **7a** and (carbethoxymethylene)triphenylphosphorane in dry xylene was refluxed for 13 hours to obtain the linear benzocoumarin (**10**). 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 contained some uncyclised product, it was as such subjected to cyclisation in presence of *para*-toluenesulfonic acid (*p*-TSA) in dry benzene using a Dean-Stark separator to furnish 3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-2-one (**11**). 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 acyclic product, it was again subjected to cyclisation in presence of *p*-TSA in dry benzene, using a Dean-Stark separator as before, to afford the desired linear dihydronaphthopyran (**6a**) in overall 40% yield over four steps. Similarly, the angular dihydronaphthopyrans **3b** (36%) and **4** (41%) were synthesised (Scheme 1) from 1-methoxy-2-naphthaldehyde (**8**) and 2-methoxy-1-naphthaldehyde (**9**) respectively.

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

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Techniques used: IR, ^{1}H-NMR, elemental analyses, TL and column chromatography.

References: 26

Schemes: 2

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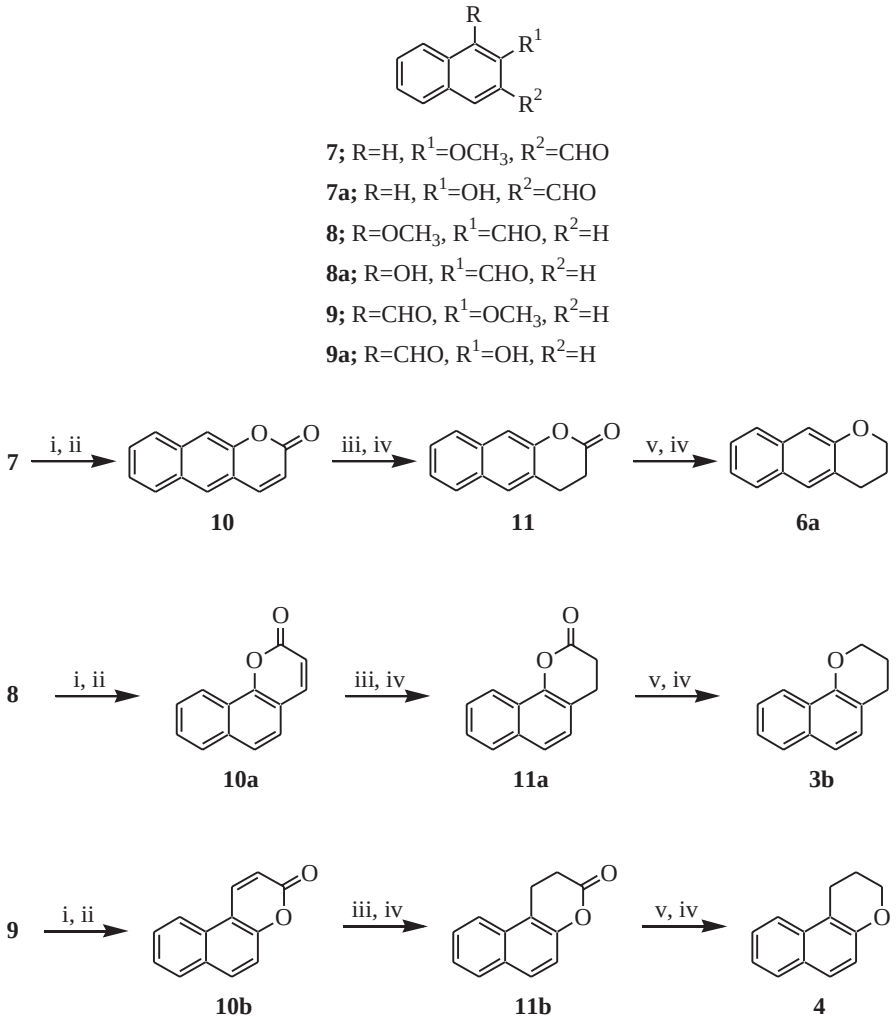

Scheme 1 Reagents and conditions: (i) $AlCl_3$-CH_2Cl_2, stir, R.T., 1h; (ii) $Ph_3P{=}CHCOOC_2H_5$, dry xylene, reflux, 13h; (iii) Ni-Al, 20% aq. NaOH, 80-90ºC, stir, 1h; (iv) p-TSA, dry benzene, reflux, 1h; (v) $LiAlH_4$, dry Et_2O, stir, R.T., 1h.

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