Aromatic Ring Formation by the 1,3-Michael-Claisen Annulation: Total Synthesis of Sophorapterocarpan A, Maackiain, and Anhydropisatin

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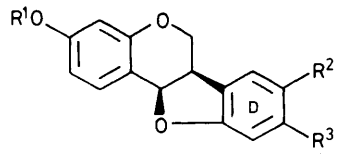
The utility of the 1,3-Michael–Claisen annulation sequence in the synthesis of natural products has been demonstrated by the synthesis of sophorapterocarpan A (**1**), maackiain (**2**), and anhydropisatin (**3**).

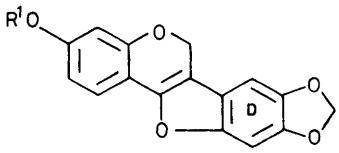
Annulations leading to aromatic rings are of great importance in the synthesis of natural products and biologically active compounds.[1] In this communication we outline an effective synthetic approach to sophorapterocarpan A (**1**), maackiain (**2**), and anhydropisatin (**3**)[2] using a three carbon [methylenelactone (**4**) or (**5**)] plus three carbon [ketone (**6**) or (**7**)] annulation based on a 1,3-Michael–Claisen condensation.

The methylenelactone (**4**), chosen as a starting material, was prepared from 7-hydroxychroman-4-one[3] *via* seven steps.[4] The ketone (**6**) was obtained from 1-(phenylthio)propan-2-one[5] *via* two steps. The [3C + 3C] annulation was achieved by condensation of (**4**) (1 equiv.) with (**6**) (1 equiv.) in dimethoxyethane (DME) in the presence of NaH (1 equiv.) at room temperature. The unstable acidic extract thus produced was heated in benzene to afford the pterocarpan framework (**8**) in 25% total yield. The acetate (**9**) obtained from (**8**) was debenzylated by treatment with trichloroborane[6] in dichloromethane at −50 °C for 5 min to afford the phenol (**10**) in 57% yield. Hydrolysis of (**10**) with NaOH in MeOH–H_2O produced (±)-sophorapterocarpan A (**1**) in 65% yield, m.p. 52—55 °C. The spectral data and the chromatographic behaviour of (**1**) were identical with those of an authentic specimen.[7]

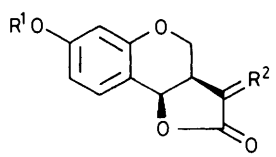
Maackiain (**2**) and anhydropisatin (**3**) have a 1,2,4-trioxybenzene structure in their D rings which was constructed by the annulation[8] using the methylenelactones (**4**, **5**) and 1,1-bis(ethylthio)propan-2-one (**7**).[9] Reaction of (**4**) (1 equiv.) with (**7**) (1 equiv.) in DME in the presence of NaH (1 equiv.) at room temperature gave two tautomers in 62% yield which were separated by SiO_2 chromatography (1% MeOH–CH_2Cl_2) [enol isomer (**11a**): keto isomer (**11b**) 2:1]. Treatment of each isomer with mercuric perchlorate (MPC)[10] in $CHCl_3$–tetrahydrofuran (THF) followed by refluxing in acetic acid afforded the pterocarpan structure (**12**) [44% from (**11a**) and 52% from (**11b**), respectively]. Methylenation of (**12**) with dibromomethane in the presence of caesium fluoride[11] in DMF at 110 °C unexpectedly gave the dehydrogenated compound (**13**) in 63% yield, m.p. 164—165 °C (lit.[12] m.p.



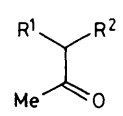
(**1**) R^1 = H, R^2 = $CH_2CH{=}CMe_2$, R^3 = OH
(**2**) R^1 = H, R^2, R^3 = OCH_2O
(**8**) R^1 = $PhCH_2$, R^2 = $CH_2CH{=}CMe_2$, R^3 = OH
(**9**) R^1 = $PhCH_2$, R^2 = $CH_2CH{=}CMe_2$, R^3 = OAc
(**10**) R^1 = H, R^2 = $CH_2CH{=}CMe_2$, R^3 = OAc
(**12**) R^1 = $PhCH_2$, R^2 = R^3 = OH
(**16**) R^1 = Me, R^2 = R^3 = OH

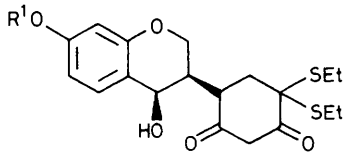


(**3**) R^1 = Me
(**13**) R^1 = $PhCH_2$



(**4**) R^1 = $PhCH_2$, R^2 = CH_2
(**5**) R^1 = Me, R^2 = CH_2
(**14**) R^1 = Me, R^2 = H_2





(**6**) R^1 = S(O)Ph, R^2 = $CH_2CH{=}CMe_2$
(**7**) R^1 = R^2 = SEt

(**11**) R^1 = $PhCH_2$
(**15**) R^1 = Me

167—168 °C). Compound (**13**) has already been converted to maackiain (**2**) by a reductive procedure,[12] so our synthesis of (**13**) constitutes a formal synthesis of (**2**).

It is of interest that dehydrogenation took place during the methylenation reaction, leading to an effective synthesis of anhydropisation (**3**). The methylenelactone (**5**) chosen as a starting material was prepared from the lactone (**14**).[1b] Reaction of (**5**) with (**7**) under the same conditions as before gave two tautomers in 48% yield which were separated by SiO_2 chromatography (1% MeOH–CH_2Cl_2) [enol isomer (**15a**): keto isomer (**15b**) 5 : 1]. Each compound was converted to the diol (**16**) [55% from (**15a**) and 51% from (**15b**), respectively] by treatment with MPC and then, acetic acid. Reaction of (**16**) with dibromethane under the same conditions as for (**12**) gave (**3**) in 68% yield, m.p. 183—185 °C. The spectral data and the chromatographic behaviour of (**3**) were identical with those of the authentic specimen.[13]

This 1,3-Michael–Claisen condensation utilizing three carbon units illustrates a hitherto undeveloped approach to aromatic natural products.

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