# A Facile Route to the Benzooxabicyclo[3.2.1]octane (2,3,4,5-Tetrahydro-2,5-methano-1-benzoxepine) System: Application to a Short Synthesis of Filiformin

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Photolytic ethylene addition to 3-methoxychromones **3a–c** furnished the 3-hydroxyoxetanes **4a–c**; reduction to the diols **5a–c** followed by acid-catalysed rearrangement afforded the benzooxabicyclo[3.2.1]octanones **6a–c** and bromination of **6c** furnished **7**, which has previously been converted to filiformin **2**.

The benzooxabicyclo[3.2.1]octane ring system **1** is featured in the marine sesquiterpene filiformin **2**[1] and congeners. The oxabicyclo[3.2.1]octane unit itself is present in the trichothecenes,[2] the well-known group of sesquiterpene antibiotics. The A-ring aromatic analogues[3] of these compounds enclosing the basic tricarbocyclic unit **1** have also been reported to display significant biological activity. The few efforts made at development of the ring system **1** leading to synthesis of **2**[4,5] have involved multistep transformations and relatively poor yield. We present an expeditious and convenient protocol for the benzooxabicyclo[3.2.1]octane system, through the expediency of a pinacol rearrangement in a substrate prepared in two steps from readily available chromone precursors. The methodology is characterised by simple reaction conditions and high yields, and has been applied to a short synthesis of filiformin **2**. Further, it may also be extendable to the trichothecene ring system.

Irradiation of a benzene solution of **3a** with a continuous flow of ethylene furnished **4a**† as the sole isolated product in 73% yield. This is deemed to arise from the intermediate photoadduct in which the photoexcited ketone abstracts a hydrogen atom from the methoxy group leading to a 1,4-biradical **X**. Radical recombination then leads to the 3-hydroxyoxetane **4a**. Abstraction of γ-hydrogen in the photolysis of α-methoxy ketones to produce 3-hydroxyoxetanes is well precedented[6] and the tandem cycloaddition and γ-hydrogen abstraction in alkene addition to α-methoxy enones has also been reported.[7] The structure of **4a** was assigned from $^1$H NMR spectroscopy where it displayed a two-proton AB quartet at δ 4.43 and 4.56 for the 3-hydroxyoxetane methylene group and a singlet at δ 2.81 for the hydroxy proton. The *cis* addition of ethylene to the chromone followed our previous results,[8] and the configuration of the 3-hydroxyoxetane has been assigned based on analogy with cognate systems.[7] Chromones **3b** and **3c** also displayed identical behaviour affording **4b**‡ and **4c**, respectively, in very good yields. Similar photolytic addition to **3d** furnished the cyclobutanol **4d**.

Compounds **4a–c** enclose an α-hydroxycyclobutane function. This was expected to serve as a progenitor of a cyclopentanone (bridged or fused), which may be revealed through an acid-catalysed rearrangement. The potential of 3-hydroxyoxetane as a convenient handle in a synthetic pathway is yet to be exploited. Initial efforts at direct acid-catalysed rearrangement of **4a** led to a complex product profile. Hence, keeping further investigations in abeyance, a modification was introduced. Compound **4a** was reduced with lithium aluminium hydride in refluxing THF (tetrahydrofuran) to furnish the diol **5a** in 94% yield, most suited for a pinacol rearrangement. Previously we had reported[8] the acid-catalysed rearrangement of cyclobutachromanols in connection with a short synthesis of the marine sesquiterpene aplysin. Following on from this the rearrangement of **5a** was initially tried using boron trifluoride ethereate ($BF_3$·$Et_2O$) as catalyst. In the event, treatment of a benzene solution of **5a** with $BF_3$·$Et_2O$ at ambient temperature for 1 h resulted in complete rearrangement to furnish **6a**, IR 1765 cm$^{-1}$; as the only isolated product in 85% yield resulting from exclusive peripheral bond migration. Similar reduction and rearrangement of **4b** and **4c** also resulted in production of the bridged ketones **6b** and **6c**, respectively, in excellent yields (Scheme 1). Thus, the sequence of reactions has provided an efficient and convenient access to **1**.

The synthesis of filiformin **2** was completed by bromination of **6c** to furnish the bromoketone **7**,[4] identical with an authentic sample by m.p. and spectral comparison. Conversion of **7** to filiformin has previously been reported[4] and thus concluded in the present instance a short, expeditious route to this compound. Since the bromoketone **7** has also been converted to aplysin,[4] the present synthesis of **7** provided another approach to this marine sesquiterpene.

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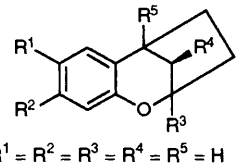
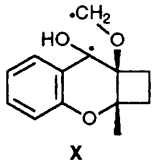


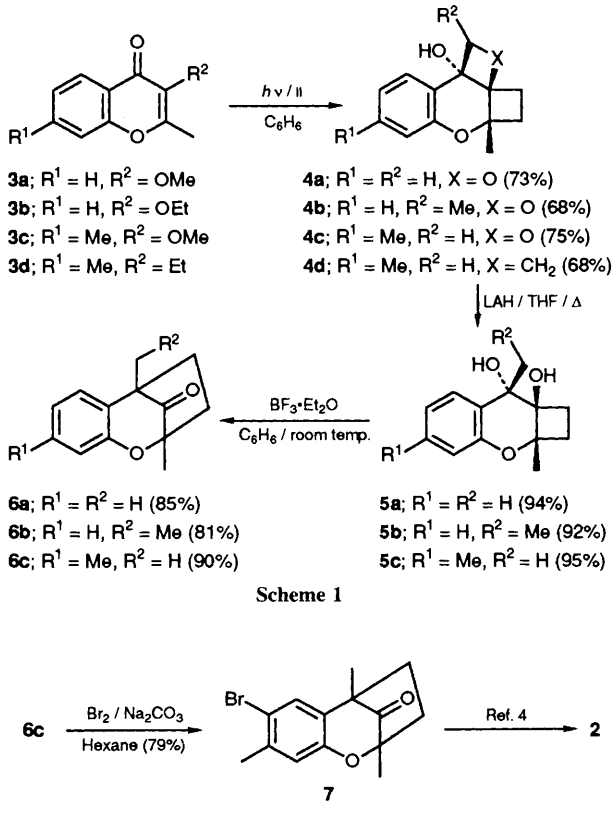
**1**; $R^1 = R^2 = R^3 = R^4 = R^5 = H$
**2**; $R^1 = Br$, $R^2 = R^3 = R^4 = R^5 = Me$



**X**

† All compounds reported here gave spectral and analytical data consistent with assigned structures.

‡ The configuration of the secondary methyl group is undefined. However, it was not considered important for subsequent reactions.




**Scheme 1**

for the high resolution $^1H$ NMR and $^{13}C$ NMR spectra of some of the compounds reported here and Professor David J. Goldsmith, Department of Chemistry, Emory University, Atlanta for the comparison $^1H$ NMR spectra of our synthetic **7** with that of an authentic sample A. N. also thanks the CSIR, New Delhi for a research fellowship.

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