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Adventures in heterocycle chemistry: The oxa-Michael cascade for the synthesis of complex natural products and highly functionalized bioactive compounds

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This is an account of the award lecture given by Stefan Bräse on the occasion of the ISCB AWARD FOR EXCELLENCE 2009 of the Indian Society of Chemical Biologists, held in Delhi in January 2009. The domino reaction between salicylaldehydes and α,β-unsaturated aldehydes is a common method to obtain a great variety of oxygen-heterocycles like cannabinoids, chromenes, and coumarins. This reaction enables also the synthesis of mycotoxins such as diversonol, the blennolides and secalonic acids.

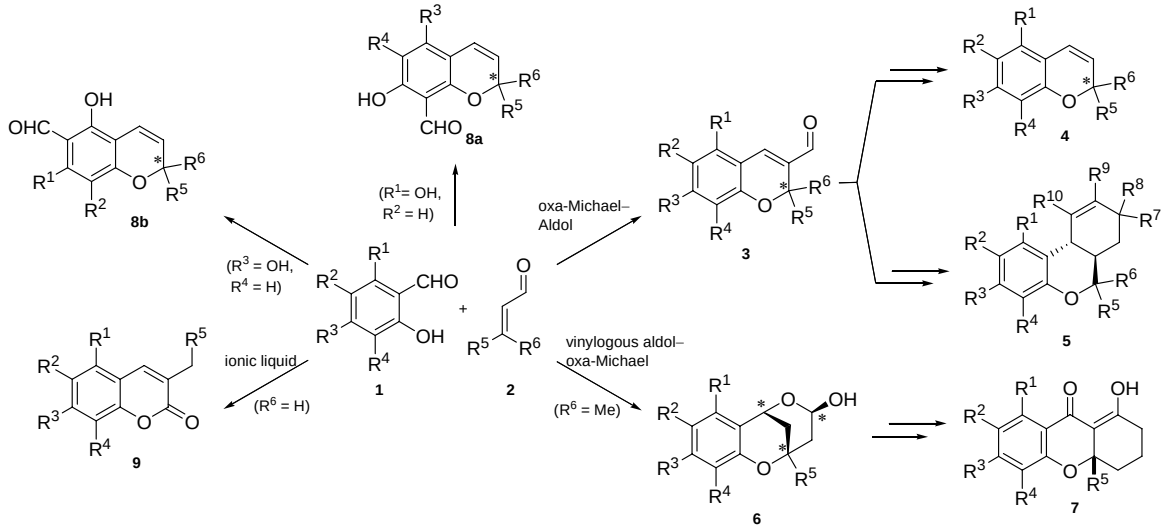
Keywords: Oxygen-heterocycles, domino oxa-Michael-Aldol reaction, coumarins, chromenes, natural products, cannabinoids

Biologically active compounds are often derived from heterocyclic structures, which are frequently found in natural and synthetic products[1]. These heterocyclic compounds often show a great variety of pharmacological properties. For this reason the synthesis of heterocycles plays an important role in organic chemistry as well as in the drug discovery process in particular[2].

Nearly ten years ago, we initiated a program for the synthesis of complex natural products and other bioactive compounds. The focus in this account describes our adventure within the benzoannelated-oxygen-heterocycles.

The domino oxa-Michael-Aldol reaction[3] between salicylaldehydes **1** and α,β-unsaturated aldehydes **2** is a versatile reaction leading to a variety of heterocyclic products (**Scheme I**).

It was in 2003, when Bernhard Lesch - the first diploma student of our group at the University of Bonn - discovered the reaction of salicylaldehydes with cyclohexenones[4]. This reaction is applicable to a variety of salicylaldehydes and cyclohexenones and



Scheme I — Reaction of salicylaldehydes **1** and α,β-unsaturated aldehydes **2**

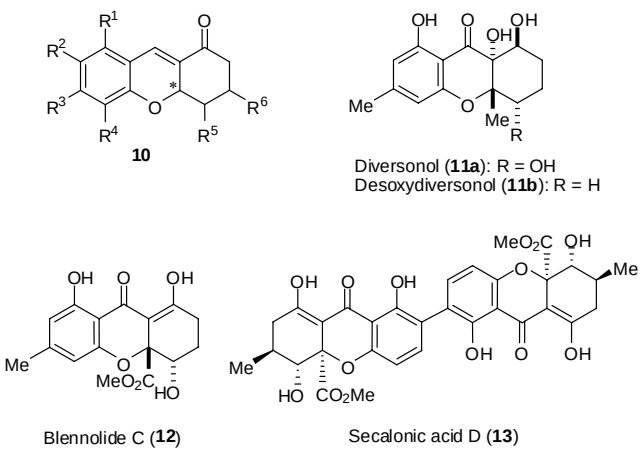


Figure 1 — Examples for highly substituted xanthones

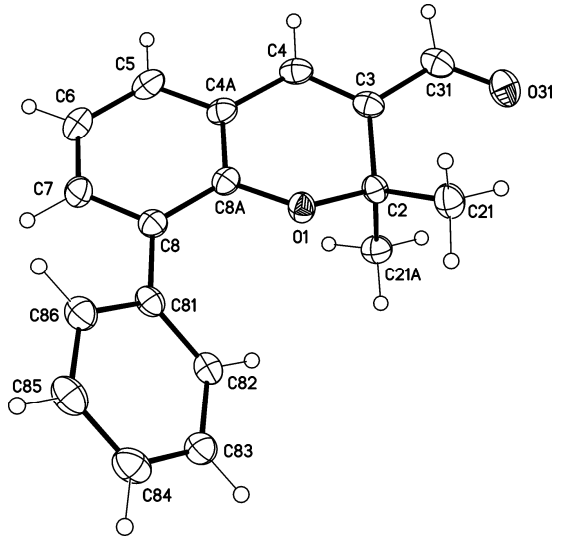


Figure 2 — X-Ray structure of a formyl chromene **3 [SB032]** (R^4 = Ph; R^5,R^6 = Me) (displacement parameters are drawn at 50% probability level)[15].

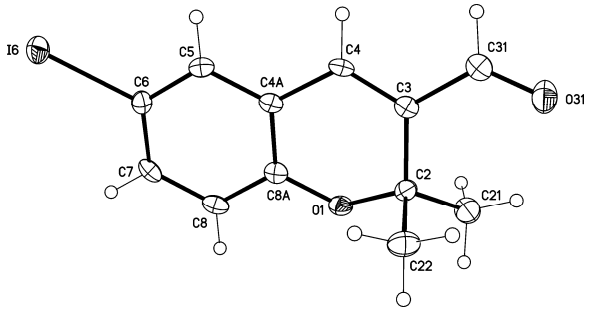


Figure 3 — X-Ray structure of a formyl chromene **3** [SB119_HY] (R^2 = I; R^5,R^6 = Me) (displacement parameters are drawn at 50% probability level)[15].

delivers highly functionalized xanthones **10** (**Figure 1**) (ref. 5). In the meantime; we used this reaction for the total synthesis of fungal natural products namely Diversonol **11a** and Blennolide C (**12**, ref.6). We also made significant contributions towards the synthesis of the fungal metabolites secalonic acids such as **13** (**Figure 1**).

However, α,β-unsaturated aldehydes **2** react in a yet more diverse fashion with salicylaldehydes (**Scheme I**). Depending on the reaction conditions, an oxa-Michael–Aldol reaction occurs leading to 3-formyl-2*H*-chromenes **3** (**Figures 2** to **5**, ref.7-9) We used these molecules for the synthesis of chromenes **4** by a rhodium-catalyzed deformylation reaction (**Scheme I**, ref.10) In addition, formyl chromenes **3** can also be converted into THC-like molecules **5** *via* an asymmetric Wittig-Diels-Alder sequence (**Scheme I**, ref. 7b).

2*H*-Chromenes **8** with a different substitution pattern are available from this cascade if resorcylaldehydes were used. While 2-formyl resorcin derivatives

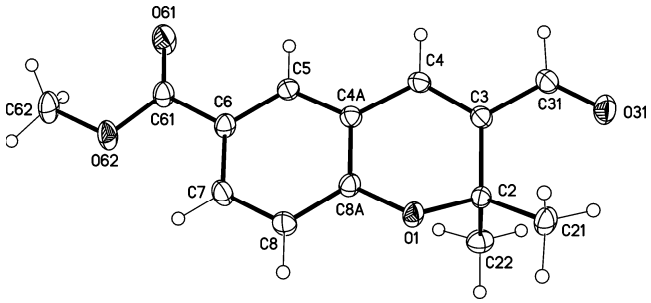


Figure 4 — X-Ray structure of a formyl chromene **3 [SB114_HY]** (R^2 = CO_2Me; R^5,R^6 = Me) (displacement parameters are drawn at 50% probability level) [15].

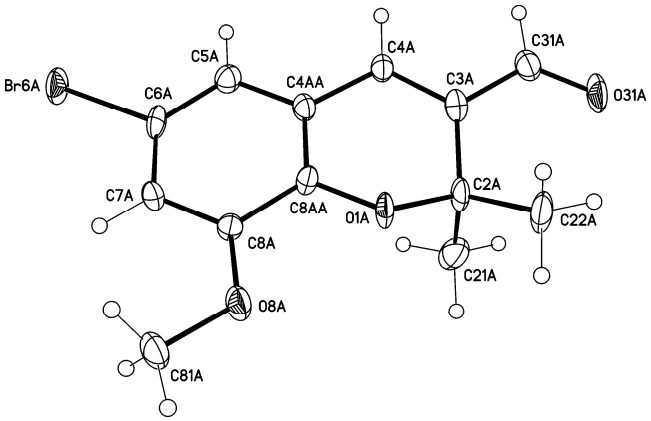


Figure 5 — X-Ray structure of a formyl chromene 3 [SB101_HY] (R^2 = Br; R^4 = OMe; R^5,R^6 = Me), one of the four crystallographic independent molecules (displacement parameters are drawn at 50% probability level)[15].

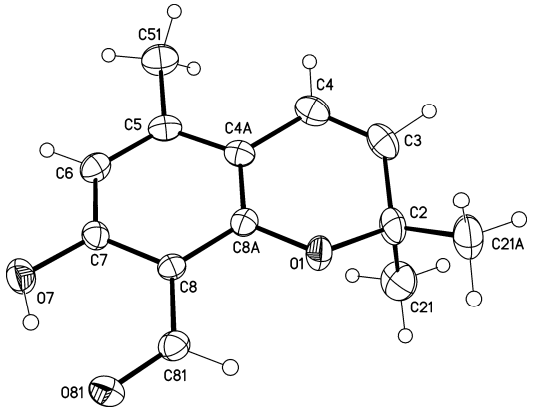


Figure 6 — X-Ray structure of a chromene **8a [SB031]** (R^1 = Me; R^3 = Me; R^5,R^6 = Me) (displacement parameters are drawn at 50% probability level) [15].

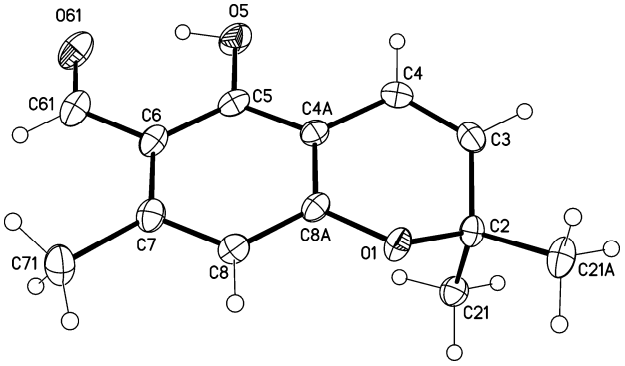


Figure 7 — X-Ray structure of a chromene **8b [SB030]** (R^1 = Me; R^3 = OH; R^5,R^6 = Me) (displacement parameters are drawn at 50% probability level)[15].

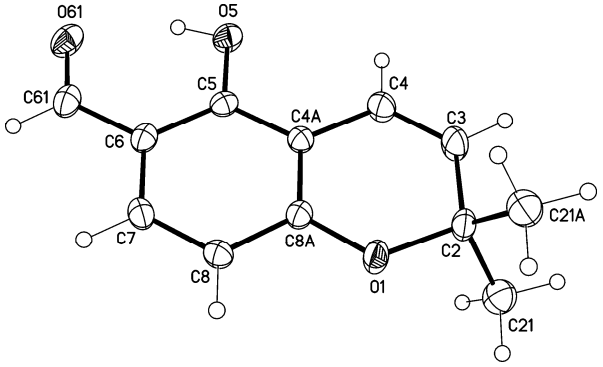


Figure 8 — X-Ray structure of a chromene 8b [SB019] (R^3 = OH; R^5,R^6 = Me), the molecule possesses crystallographic C_s-symmetry (displacement parameters are drawn at 50% probability level)[15].

1 (R^1 = OH) gave chromenes of type **8a** (**Figure 6**), 4-formyl derivatives **1** (R^3 = OH) yielded chromenes of type **8b** (**Figures 7**,**8**).

Very puzzling, prenal and other similar aldehydes were converted under the yet same conditions into

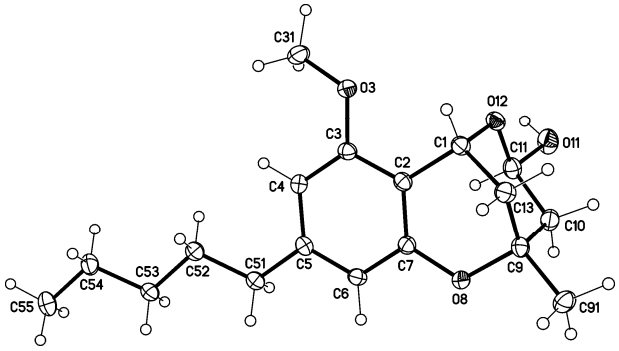


Figure 9 — X-Ray structure of a lactol **6 [SB103_HY]** (R^1 = OMe; R^3 = Pentyl; R^5 = Me) one of the two crystallographic independent molecules (displacement parameters are drawn at 50% probability level)[15].

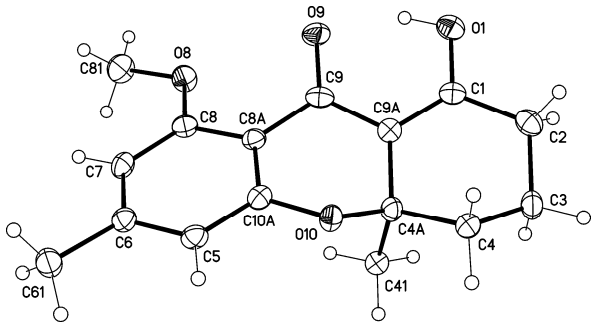


Figure 10 — X-Ray structure of a tetrahydroxanthone **7 [SB081_HY]** (R^1 = OMe, R^3,R^5 = Me), a precursor of Desoxydiversonol (**11b**) one of the two crystallographic independent molecules (displacement parameters are drawn at 50% probability level)[15].

vinylogous enolates which at the end react with the salicylaldehydes in a vinylogous Aldol–oxa-Michael cascade to give lactols **6** having three stereogenic centers as single diastereomers (**Figure 9**, ref. 7,11,12).

After optimization of this sequence, we developed a short and efficient route to convert these lactols to tetrahydroxanthones **7** (ref.11).

Figure 10 shows the X-Ray structure of a precursor **7** (R^1 = OMe, R^3, R^5 = Me) of desoxy-diversonol **11b** which was synthesized using this route and three further steps using a sequence described by Tietze and co-workers[13].

However, if the reaction of simple and substituted α,β-unsaturated aldehydes **2** and salicylaldehydes **1** is carried out in the presence of ionic liquids having imidazolium groups, a NHC-promoted Umpolung reaction of the α,β-unsaturated aldehydes **2** takes place leading to the formation of 3-alkylcoumarins **9**

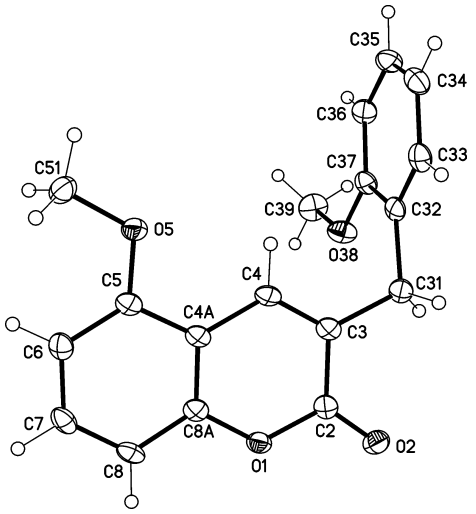


Figure 11 — X-Ray structure of a coumarin 9 [SB062_HY] (R^1 = OMe; R^5 = *o*-$MeOC_6H_4$) (displacement parameters are drawn at 50% probability level) [15].

(**Scheme I**, **Figure 11**) in good overall yields[14]. The reaction in ionic liquids also facilitates the work-up due to a simple extraction process. The coumarins obtained have shown certain acitivity against the cannabinoid receptors CB1 and CB2 (ref. 14b).

Conclusion

This account has given ample evidence that the oxa-Michael cascade developed in our laboratories has turned into a useful synthetic tool over the recent years. Major progress has been made in terms of substrate scope and the development of efficient protocols. Moreover, high levels of stereocontrol can be achieved by using chiral organocatalysts. All these developments have led to expanding use of the oxa-Michael cascade in the field of total synthesis of cannobinoids and the reaction even turned out to be a key tool for the preparation of highly substituted xanthones.

Acknowledgements

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15 Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the

Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 735794 (**SB032**), CCDC 735795 (**SB119_HY**), CCDC 735796 (**SB114_HY**), CCDC 735797 (**SB101_HY**), CCDC 258380 (**SB031**), CCDC 258382 (**SB030**), CCDC 258381 (**SB019**), CCDC 735798 (**SB103_HY**), CCDC 735799 (**SB081_HY**), and 735800 (**SB062_HY**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int.code+(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).