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Biomimetic synthesis of nudicaulins I and II, yellow pigments from the Iceland poppy *Papaver nudicaule*†

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Indole and the anthocyanin orientalin proceed through a unique cascade sequence that leads to nudicaulins I and II in 92% yield. This biomimetic synthesis confirms the biosynthesis proposal for these structurally unprecedented flavoalkaloids that play a key role in the colour range displayed by the Iceland poppy.

The petals of the Iceland poppy (*Papaver nudicaule*) display colours ranging from red and orange to dark and light yellow.[1] The pigments responsible for the red colouration[2] are the anthocyanins pelargonidin 3-*O*-β-sophoroside-7-*O*-β-glucoside (orientalin; **1**), pelargonidin-3-*O*-β-sophoroside (**2**) and pelargonidin 3-*O*-β-[(6-malonyl)sophoroside] (**3**) (Fig. 1A).[3,4] The structural assignment of the pigment responsible for the orange and yellow colours, termed nudicaulin, has been the subject of multiple investigations over many years since its isolation was first reported by Robert Robinson.[5–7] In 2013, Bringmann, Schneider and co-workers[8] finally solved this decades-old conundrum and reported that nudicaulin is a diglycosylated pentacyclic dihydrobenzofurocyclopentaindole that exists as a mixture of C3–C11 *cis*-fused diastereomers, termed nudicaulins I and II (**4a** and **4b**) (Fig. 1B).[9]

From a biosynthetic perspective, the nudicaulins are fascinating. The nudicaulins are flavoalkaloids, a rare class of natural products,[10] that possess a β-glucoside at C7-OH and a β-sophoroside at C11-OH that correspond to the substitution pattern in orientalin (**1**). It is therefore logical to assume that the pelargonidin glycosides and the nudicaulins are biosynthetically related. Through a series of labelling studies,[11,12] Schneider and co-workers showed that the nudicaulin framework is assembled *in vivo* from indole and kaempferol-3-*O*-β-sophoroside-7-*O*-β-glucoside, the biosynthetic flavonol precursor to orientalin (**1**). Furthermore, the level of anthocyanins (red) decreases as the level of nudicaulin (yellow) rises in the flower and the same colour change is observed when red petals are exposed to an aqueous solution of indole.[13,14]

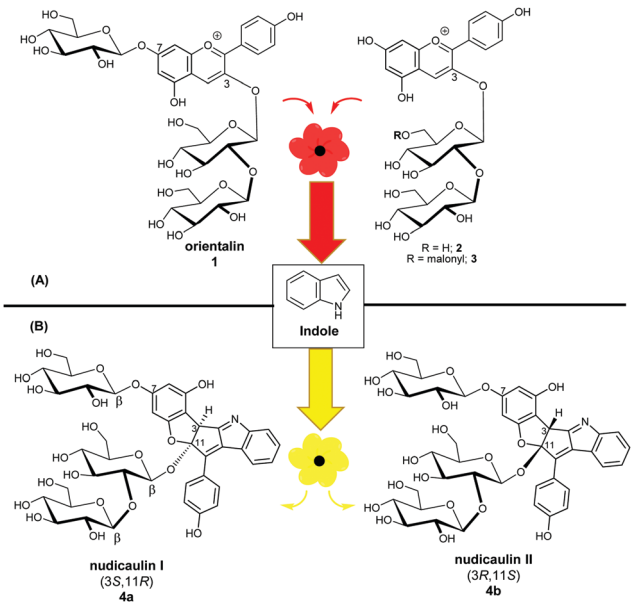

Fig. 1 Pigments responsible for the range of colours displayed by the Iceland poppy (*Papaver nudicaule*).

A plausible biosynthesis[12] of the nudicaulins is shown in Scheme 1A. Nucleophilic attack by indole onto the orientalin C2-site[15] followed by retro-6π-electrocyclic ring opening would generate the quinone methide **5**. Diastereoselective biscyclisation would form the *cis*-fused 5,5-ring system[16] that upon dehydrogenation would generate nudicaulins **4a** and **4b**. This cascade process was recently shown to be viable; the quercetin-derived anthocyanidin **6** was converted to the racemic nudicaulin aglycons **7** upon reaction with several indoles under acidic conditions (Scheme 1B).[13] However, the yields for this process are poor, an excess of the indole partner is required and the products do not contain the correct substitution pattern nor the glycosides present in the nudicaulins.

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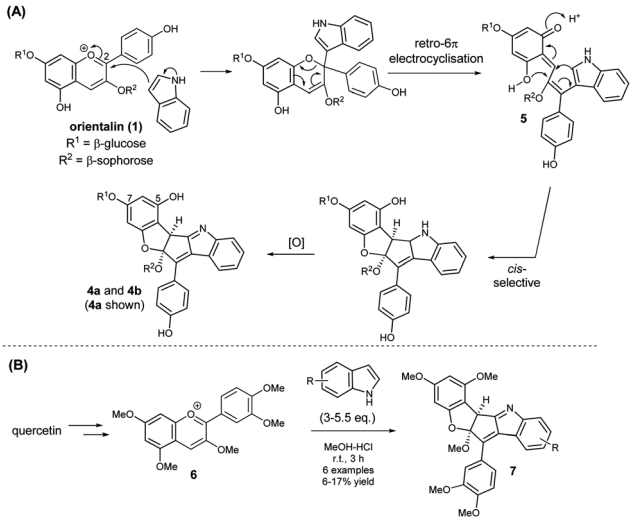
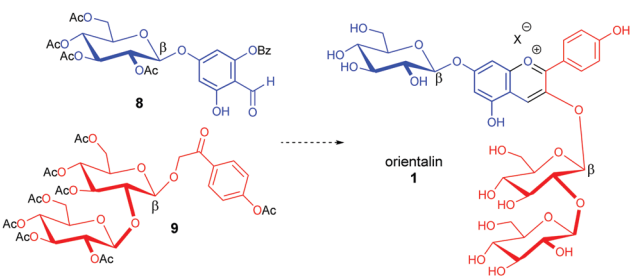


Scheme 1 (A) Proposed biosynthesis of nudicaulin; (B) synthesis of the nudicaulin aglycon.[13]

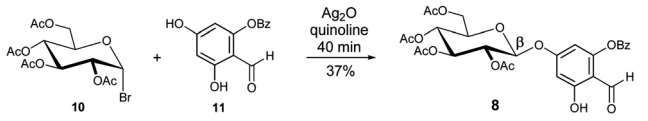
In view of our ongoing interest in biomimetic synthesis[17] and flavoalkaloids,[18] we were intrigued by the biosynthesis proposal for the nudicaulins and instigated a programme to validate this cascade process depicted in Scheme 1A. This study required access to orientalin (**1**), a diglycosylated anthocyanin not previously synthesised. It was assumed that orientalin would be accessible by the condensation of the phloroglucinaldehyde **8** and the acetophenone **9** harbouring the requisite β-glucoside and β-sophoroside units, respectively (Scheme 2).[19,20]

The simpler glycoside **8** was the initial target. The β-selective glycosylation of the commercially available donor 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**10**) with the known phloroglucinaldehyde **11**[21] proceeded with the desired regioselectivity in the presence of silver(I) oxide and quinoline[22] to give β-glycoside **8** (Scheme 3).

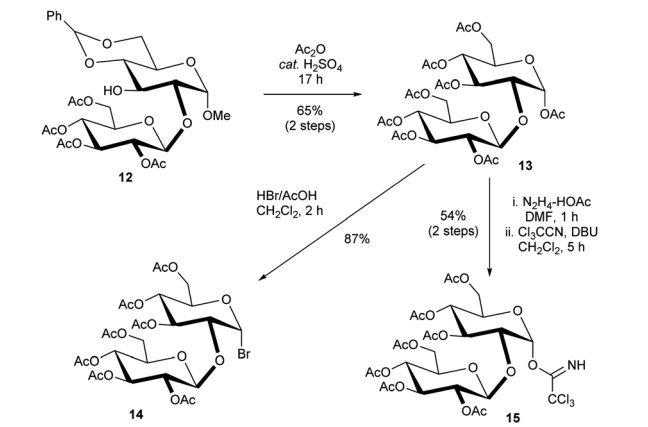
Due to propensity for sophorose donors to undergo α-glycosylation with unreactive acceptors in the absence of neighbouring group effects,[23] it was anticipated that the diastereoselective synthesis of the β-sophoroside **9** would require more than one donor to be screened (Scheme 4). Treatment of the 1,2-glucoside **12**[24] with acetic anhydride in the presence of catalytic quantities of sulfuric acid gave octaacetylsophorose **13** that was readily converted into the two sophorose donors, α-bromide **14** and the α-trichloracetimidiate **15**[25] in good yield.



Scheme 2 Proposed synthesis of orientalin (**1**).

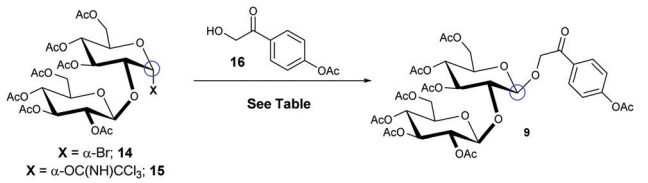


Scheme 3 Regioselective β-glycosylation of phloroglucinaldehyde **8**.



Scheme 4 Synthesis of sophorose donors **14** and **15**.

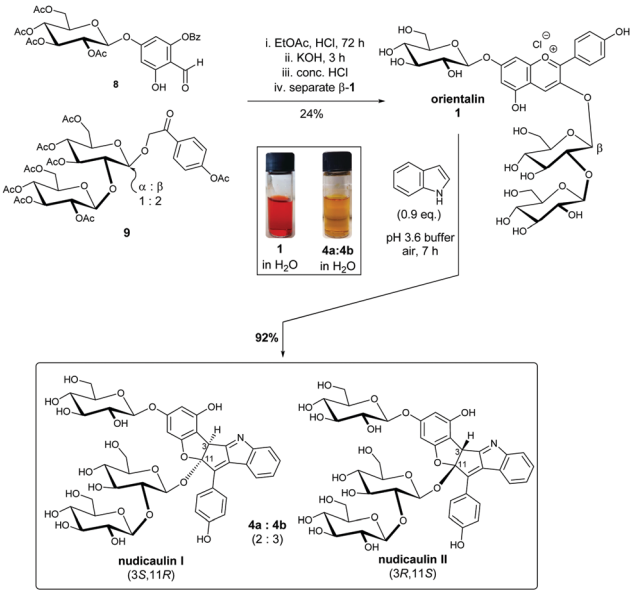
Table 1 Glycosylation of sophorose donors **14** and **15** with acceptor **16**



Entry	Donor	Activator (eq.)	Solvent	Temp. (°C)	Time (h)	Yield 9 (α : β)
1	**14**	Ag_2CO_3 (2)	CH_2Cl_2	rt	43	—
2	**14**	$BF_3{\cdot}Et_2O$ (1)	CH_2Cl_2	−41 → rt	24	—
3	**15**	$BF_3{\cdot}Et_2O$ (0.5)	CH_2Cl_2	−41 → rt	2	24% 2 : 1
4	**15**	TMSOTf (0.5)	CH_2Cl_2	−41 → −20	0.8	99% α only
5	**15**	**TMSOTf (0.5)**	**MeCN**	**−41**	**0.25**	**74% 1 : 2**
6	**15**	TMSOTf (0.5)	EtCN	−41	0.5	28% 1 : 1
7[a]	**15**	TMSOTf (0.5)	MeCN	−41	0.25	Trace ND
8	**15**	$Pd(MeCN)_4(BF_4)_2$ (0.2)	CH_2Cl_2	−41 → rt	24	16% 1 : 2
9	**15**	$Pd(MeCN)_4(BF_4)_2$ (1)	CH_2Cl_2	rt → 40	17	24% 1 : 2
10[a]	**15**	$Pd(MeCN)_4(BF_4)_2$ (1)	CH_2Cl_2	rt	24	Trace ND
11	**15**	$AuCl_3$ (0.1)	CH_2Cl_2	−78 → rt	1	60% 1 : 1.3

[a] Reverse mode addition.

With the sophorose donors **14** and **15** in hand, β-glycosylation with the hydroxyacetophenone **16**[26] as acceptor could be investigated (Table 1). The sophorose donor **14** has been reported to undergo β-selective glycosylations with reactive secondary alcohols in the presence of silver carbonate,[25] but applying these conditions using the less reactive hydroxyacetophenone **16** failed (entry 1). The two donors **14** and **15** were subsequently screened in the glycosylation using the standard promotor $BF_3{\cdot}Et_2O$ in an effort to determine which was most suitable. The glycosylation failed using the donor **14** (entry 2), but the donor



Scheme 5 Biomimetic synthesis of nudicaulins I and II.

15 did provide the glycoside product **9** (entry 3), albeit in poor yield and as an inseparable mixture favouring the undesired α-anomer. The sophorosyl trichloracetimidate donor **15** was deemed the more suitable substrate and was thus employed in an optimisation study. Switching the Lewis acid to TMSOTf led to a marked increase in yield, but only the α-sophoroside was formed (entry 4). Glycosylation of **15** *via* the acetonitrile derived α-nitrilium-nitrile conjugate[27] let to an anomeric mixture favouring the β-sophoroside in good yield (entry 5). This ratio decreased upon use of propionitrile (entry 6) and reverse mode addition[28] led to no reaction (entry 7). Cationic palladium(II)-catalysed glycosylation[29] gave a good ratio favouring the desired β-anomer, but in poor yield (entry 8). Attempts to improve the yield and selectivity by employing stoichiometric amounts of the palladium(II)-salt were unsuccessful (entry 9), with reverse mode addition failing to provide any improvement (entry 10). The reported β-selectivity exhibited by gold(III)-salts in glycosylations[30] partially translated onto this system, slightly favouring the formation of the β-sophoroside (entry 11). It was at this point we returned to the reaction conditions outlined in entry 5 and **9** was used as the 1 : 2 mixture in the subsequent step.

Hydrogen chloride gas was bubbled through a solution of phloroglucinaldehyde **8** and the acetophenone **9**, inducing heteroannulation to give a peracetylated orientalin derivative that upon global deprotection gave orientalin (**1**) as a bright red solid (Scheme 5). With **1** in hand, the biomimetic synthesis of the nudicaulins was attempted. A buffered solution of orientalin (**1**) and indole in an open flask went from bright red to yellow over a period of seven hours, from which the nudicaulins **4a** and **4b** were isolated in 92% yield. The product existed as a 2 : 3 mixture of C3–C11 *cis*-diastereomers favouring nudicaulin II, suggesting the sugar units are imparting modest diastereoselectivity during the biomimetic cascade process.[31] The diastereomeric ratio of **4a : 4b** was not disclosed in the isolation report, so we are unable to determine if this 2 : 3 ratio is in line with that observed *in vivo*. The 92% yield for this reaction is striking, especially considering the complexity of the biomimetic cascade and the yields obtained on simpler model systems (6–17%)[13] (Scheme 1B). The nudicaulins form yellow aqueous solutions, in line with their reported role as pigments in *Papaver nudicaule* petals.

In conclusion, the total synthesis of the flavoalkaloid pigments nudicaulins I and II has been accomplished, 80 years after their first reported isolation. The fusion of indole and the anthocyanin orientalin *via* an unprecedented biomimetic cascade affords nudicaulins I and II in excellent yield. This biomimetic synthesis verifies the biosynthesis of these pigments and provides material for colour-scent association studies.

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Conflicts of interest

There are no conflicts to declare.

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