Biomimetic Synthesis

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Biomimetic Synthesis of Santalin A,B and Santarubin A,B, the Major Colorants of Red Sandalwood**

*Sebastian Strych and Dirk Trauner**

Dedicated to the Bayer company on the occasion of its 150th anniversary

The success of organic chemistry can be largely traced back to the fascination of humans with beautiful, bright, and persistent colors. Natural dyes, such as indigo, chlorophyll, and heme, were investigated early on in the history of the field and are representative of some of its greatest achievements. William Henry Perkin's discovery of mauveine[1] and his realization of its economic potential marked the beginning of an industry that became one of the defining economic activities of the 19th century and has been closely intertwined with rapid advances in academic research. With their access to chemicals and their intellectual resources, dye companies often diversified to become producers of drugs, crop protectants, and synthetic polymers. As such, the chemistry of colorants has had an enormous impact on humanity, which continues to this day, with biological imaging and photovoltaics taking center stage.

Among the colored materials found in nature, red sandalwood caught the eye of chemists early on. This rare hardwood, obtained from the tree *Pterocarpus santalinus* and related species, has been valued for millennia, particularly in China, where it was once reserved for the furniture of the imperial household (Figure 1). It also plays an important role in Ayurveda medicine where it is used for treating digestive tract problems and coughs. Chemical investigations of its colored constituents started with Pelletier's pioneering studies in 1814.[2] Subsequent attempts at structural elucidation were complicated by the presence of many closely related isomers and congeners. Following decades of confusion regarding the positioning of phenolic hydroxy groups and their methylation patterns, the constitution of the major components, namely the santalins and santarubins, were finally settled by Arnone et al. in 1975.[3] Santalins A and B (**1**, **2**) and santarubins A and B (**3**, **4**) share a common 9*H*-benzo[*a*]xanthen-9-one core (Figure 2). They differ in the

Figure 1. Objects carved from red sandalwood (*Pterocarpus santalinus*).

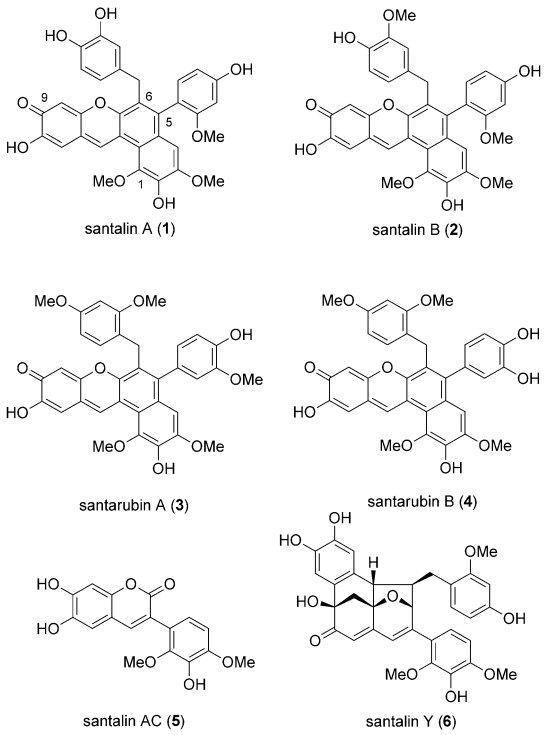

Figure 2. Colorants isolated from red hardwoods.

substitution of their phenyl substituent at C5, which can either be a resorcinol (santalins) or a catechol derivative (santarubins). The reverse is true for the benzyl substituent at position C6. In 1995, the structures of two minor components of red sandalwood, the relatively simple isoflavonoid santalin AC (**5**) and the complex yet racemic oxafenestrane santalin Y (**6**), were reported.[4]

[*] Dipl.-Chem. S. Strych, Prof. Dr. D. Trauner
Department of Chemistry and Center for Integrated Protein Science
Ludwig-Maximilians-Universität
Butenandtstrasse 5–13 (F4.086), 81377 Munich (Germany)
E-mail: dirk.trauner@lmu.de
Homepage: http://www.cup.uni-muenchen.de/oc/trauner/

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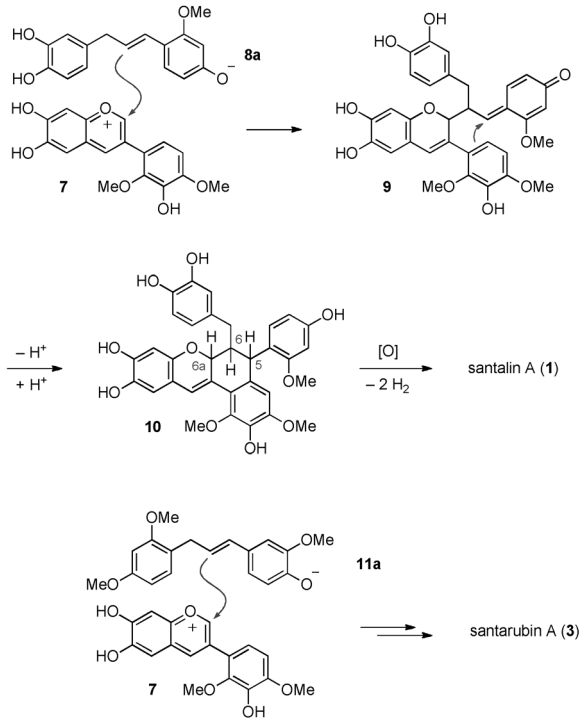
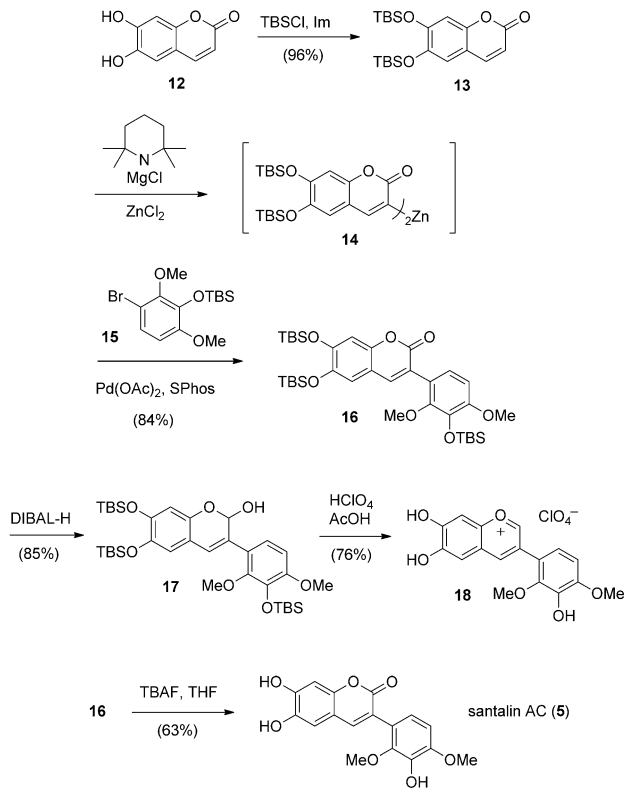
Despite the long chemical history of the santalins and santarubins, no total synthesis of the santalins and santarubins has been reported to date. We now disclose our studies on the subject, which culminated in an efficient synthesis of santalins A and B as well as santarubins A and B.

Our synthetic strategies were guided by speculations concerning the biosynthesis of these natural colorants, exemplified by santalin A and santarubin A (Scheme 1).[4] In the former case, nucleophilic attack of a benzylstyrene phenolate **8a** onto hypothetical isoflavylium ion **7** would afford a reactive intermediate, shown here as a *p*-quinone methide **9**, which would subsequently undergo Friedel–Crafts cyclization to yield compound **10**. By virtue of its labile C–H bonds at position C5, C6a, and possibly C6, and a phenolic OH bond, this intermediate would subsequently undergo facile oxidation in the presence of air to afford the benzoxanthenone santalin A. An analogous sequence involving the same isoflavylium **7** and benzylstyrene **11a** would afford santarubin A. Note that benzylstyrenes **8a** and **11a** are O-methylated to a different degree. It is also worth mentioning that an analogous nucleophilic attack of a benzylstyrene onto **7**, followed by a dearomatizing bond formation and Friedel–Crafts cyclization, could account for the formation of santalin Y.



Scheme 1. A proposed biomimetic cascade.

To explore whether this proposed biosynthetic cascade could be achieved in the absence of enzymatic catalysis, we developed a short synthesis of an isoflavone that could serve as a precursor to **7** and santalin AC. It started with esculetin (**12**), available in one operation from 1,3,4-trisacetoxybenzene and malic acid,[5] which was protected to afford bis(silyl ether) **13** (Scheme 2). Throughout our synthesis, we found



Scheme 2. Efficient access to **18** and santalin AC (**5**) using an isoflavonoid synthesis developed by Knochel and co-workers. Im = imidazol; DIBAL-H = diisobutylaluminum hydride; TBS = *tert*-butyldimethylsilyl; TBAF = tetrabutylammonium fluoride.

that protecting phenolic hydroxy groups as silyl ethers was indispensible to enable solubilization and purification of our synthetic intermediates.[6,7] By using a synthetic strategy recently published by Knochel and co-workers,[8] coumarin **13** was regioselectively deprotonated and transmetalated to afford diorganozinc species **14**, which underwent efficient cross-coupling with aryl bromide **15** in the presence of palladium acetate and Buchwald's SPhos ligand[9] to afford isoflavonoid derivative **16**. The brominated pyrogallol derivative **15** was available by silylation of the known phenol[10] (see the Supporting Information). Compound **16** could then be selectively reduced to yield lactol **17**. Upon treatment with a solution of perchloric acid in acetic acid, **17** underwent protonation and dehydration with concomitant desilylation to afford isoflavylium perchlorate **18**, which corresponds to **7** in Scheme 1. This benzopyrylium salt bearing phenolic hydroxy groups was difficult to handle, but could be purified by precipitation. The X-ray structure of **18** with the perchlorate ion hovering over the pyrylium moiety is shown in Figure 3. Alternatively, isoflavonoid **16** was deprotected under standard conditions to give synthetic santalin AC (**5**), which proved identical to the natural product.[4]

The preparation of the benzylstyrenes, necessary to obtain santalin A,B and santarubin A,B, is outlined in Scheme 3. It either involved olefin cross-metathesis[11] or Friedel–Crafts-type reactions of easily ionized alcohols.[12] To prepare santalin A, the known allylphenol derivative **19**[13] was

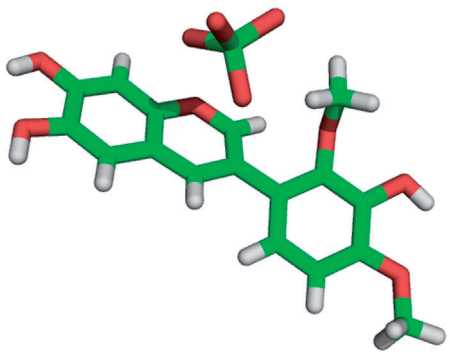
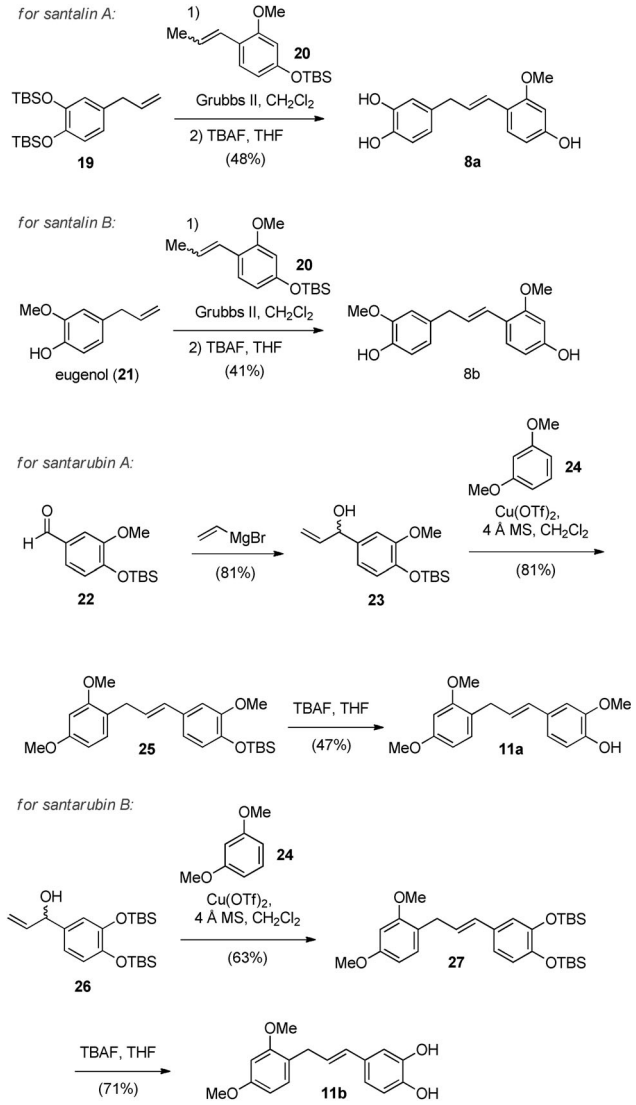


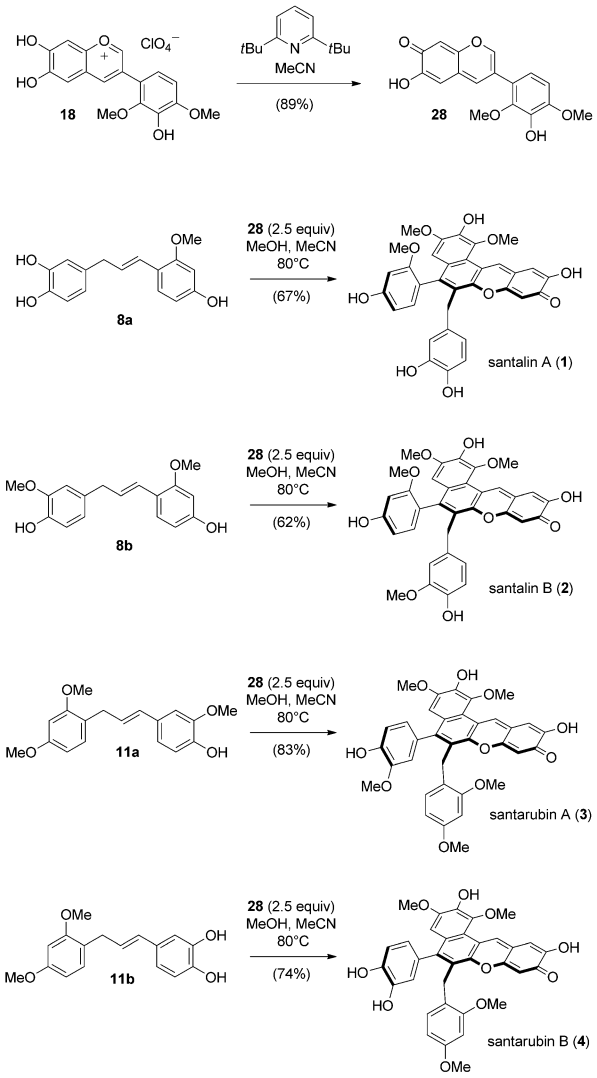
Figure 3. X-ray structure of isoflavylium perchlorate **18**. C green, H white, O red.



Scheme 3. Preparation of the benzylstyrenes **8a,b** and **11a,b**. Tf = trifluoromethanesulfonyl.

subjected to olefin cross-metathesis with styrene **20**, followed by desilylation, which gave benzylstyrene **8a** as a single diastereomer. Styrene **20** was prepared as an inconsequential 2.1:1 mixture of diastereomers through Wittig-olefination of the corresponding known aldehyde[14] (see the Supporting Information). Similarly, eugenol was subjected to olefin cross-metathesis with the same styrene **20**, followed by desilylation, to deliver building block **8b**, suitable for obtaining santalin B. To prepare santarubin A, the known benzaldehyde **22**[15] was converted into the allylic alcohol **23** by treatment with a vinyl Grignard reagent. The resulting allylic alcohol formed a stabilized cation upon treatment with $Cu(OTf)_2$,[12b] which reacted in a Friedel–Crafts-like fashion with *O*,*O*′-dimethylresorcinol **24**. Desilylation with a fluoride source then gave styrene **11a** as a single diastereomer. Similarly, the known allylic alcohol **26**[16] and resorcinol ether **24** gave styrene **27**, which upon treatment with TBAF yielded styrene **11b**, which is suitable for the synthesis of santarubin B.

With isoflavylium **18** and the various benzylstyrenes in hand, we tested the biomimetic cascade reactions. Initial attempts to effect this reaction by mixing isoflavylium perchlorate **18** with its corresponding partner in the presence of a variety of bases were met with limited success and gave complex mixtures of unidentifiable products. Eventually, we



Scheme 4. Biomimetic synthesis of santalin A,B and santarubin A,B.

found that it was important to deprotonate the isoflavylium salt **18** in a separate step, which afforded the isolable anhydrobase **28** (Scheme 4). This deprotonation was most effective when carried out by the non-nucleophilic base 2,6-bis-*tert*-butylpyridine.

We were pleased to find that mixing **28** with benzylstyrenes **8a**,**b** or **11a**,**b** gave santalins A,B and santarubins A,B, respectively (Scheme 4). These were usually isolated through precipitation and in good yields (62–83%), given the complexity of the cascade. Under optimized conditions, the reactions were carried out in the presence of air at 80°C in a methanol/acetonitrile solution by using 2.5 equivalents of the anhydrobase **28** with respect to the benzylstyrene. It thus appears that the anhydrobase not only serves to deprotonate the benzylstyrene, which simultaneously provides the nucleophile and the electrophile, but is also involved in the subsequent oxidation step. The spectroscopic data of our synthetic samples were identical in all respects with those reported for the natural products.[3]

In summary, we have developed a unified synthetic approach to the major dyes of red sandalwood, which yielded five natural products. It is yet another demonstration that complex molecular scaffolds, not easily accessible with other methods, can be assembled along biosynthetic lines without the necessity of enzymatic catalysis. The final reaction sequence appears to be general and our conditions are mild, which raises the question whether the cycloaddition/oxidation cascade could spontaneously occur in nature as well. Our studies concerning the biomimetic synthesis of santalin Y are still ongoing and will be reported in due course.

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