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Biomimetic Total Synthesis of Santalin Y**

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Abstract: *A biomimetic total synthesis of santalin Y, a structurally complex but racemic natural product, is described. The key step is proposed to be a (3 + 2) cycloaddition of a benzylstyrene to a "vinylogous oxidopyrylium", which is followed by an intramolecular Friedel–Crafts reaction. This cascade generates the unique oxafenestrane framework of the target molecule and sets its five stereocenters in one operation. Our work provides rapid access to santalin Y and clarifies its biosynthetic relationship with other colorants isolated from red sandalwood.*

The structural diversity and sophistication of natural products contributes much to the fascination they have always exerted on chemists. Metabolites that bear a multitude of stereocenters usually occur in enantiomerically pure, or at least scalemic, form. Complex natural products that are true racemates are comparatively rare. There are, however, notable exceptions, a small collection of which is shown in Figure 1. The formation of these natural products is often associated with pericyclic reactions, such as Diels–Alder reactions, which can set up to four stereocenters in a single step from achiral precursors. Electrocyclization cascades or cyclizations via ionic intermediates can lead to similar or even higher levels of complexity. The occurrence of these reactions in biosynthetic pathways has been strongly suggested by a multitude of biomimetic syntheses. Classics, such as the ones of carpanone[1] and endiandric acid A,[2] have been recently complemented by the synthesis of rubioncolin B,[3] exiguamine B,[4] and kingianin A.[5]

Another complex, yet racemic, natural product, santalin Y, occurs in "red sandalwood", the hardwood of *Pterocarpus santalinus* (Figure 2 A). The deep-red color of the highly valued material is mostly due to a series of benzoxanthenones, namely santalins A, B and santarubins A, B.[6]

The yellow pigment santalin Y, was isolated by Nohara and co-workers in 1995 as a minor component.[7] Apart from its lack of optical activity, this molecule has several structural features that makes it an attractive target for chemical

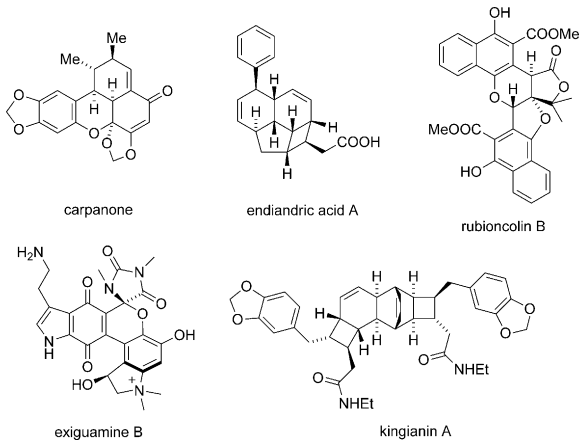

Figure 1. Complex racemic natural products that have succumbed to biomimetic synthesis.

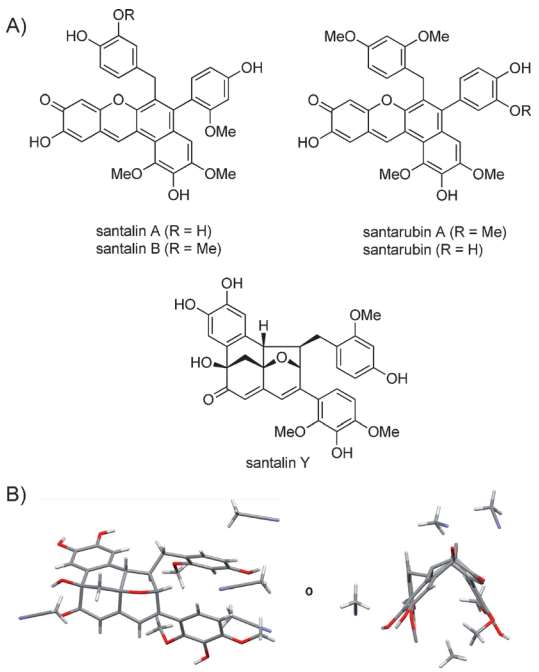

Figure 2. A) The santalins and santarubins. B) X-ray structure of santalin Y (crystallized from acetonitrile) seen from the top and the side. Some hydrogen atoms in the side view are omitted for clarity.

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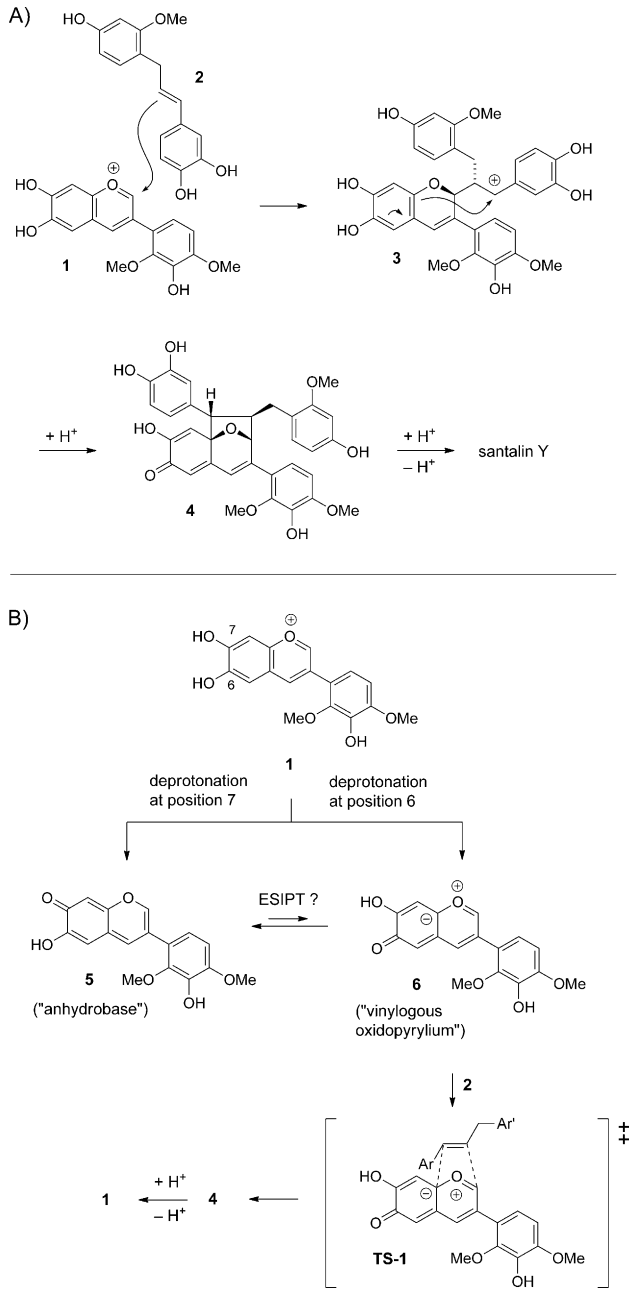
synthesis. It exhibits a unique [6,6,6,5]-oxafenestrane framework that bears a catechol moiety as well as partially methylated pyrogallol and resorcinol substituents. As seen in Figure 2 B, a bicyclic and a tricyclic ring system come together in an almost orthogonal fashion to form a "ridge" that contains three of the five stereocenters of santalin Y.

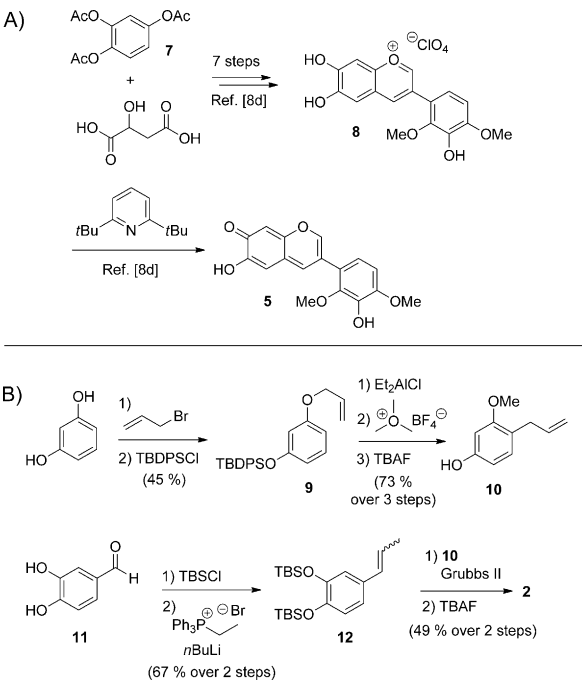
In addition to the isolation and structural elucidation of santalin Y by NMR analysis and X-ray crystallography, Nohara and co-workers provided a biosynthetic rationale for its formation.[7] According to their hypothesis, the natural product stems from an isoflavylium ion (**1**) and a benzylstyrene (**2**; Scheme 1 A). Nucleophilic attack of **2** on **1** would form a benzyl cation, shown here as diastereomer **3**, which would then undergo ring closure with concomitant dearomatization to afford a tetrahydrofuran intermediate **4**. A subsequent intramolecular Friedel–Crafts cyclization would form the tertiary alcohol and complete the biosynthesis of santalin Y.

Although this ionic cascade involves reasonable biosynthetic starting materials and reactivity patterns, the diastereoselectivities of its individual steps, as shown in Scheme 1, are not readily explained, at least in the absence of enzymatic catalysis. We, therefore, considered an alternative pathway that involves a concerted cycloaddition (Scheme 1 B). Deprotonation of isoflavylium ion **1** at position 7 would afford the anhydrobase **5** in a process that is well-precedented amongst flavonoid and isoflavonoid plant pigments.[8] Alternatively, the deprotonation of **1** at position 6 would yield a "vinylogous oxidopyrylium" **6**. At the outset of our studies it was not clear whether this deprotonation would be energetically viable under thermal conditions. We hypothesized that the formation of **6** would require a photochemically triggered excited-state intramolecular proton transfer (ESIPT) of **5**. The analogous formation of oxidopyrylium species by ESIPT, followed by cycloadditions, has been studied in detail by Porco and co-workers, and has been recently used in a total synthesis of rocaglamides.[9] Once the vinylogous oxidopyrylium **6** is formed, it would undergo a stereospecific 1,3-dipolar cycloaddition that would again afford **4** and, after Friedel–Crafts closure of the final ring, santalin Y (**1**).

In previous studies on the biomimetic synthesis of santalins A, B and santarubins A, B, we described an efficient synthesis of both isoflavylium salt **8** and anhydrobase **5**.[8d] This synthesis, summarized in Scheme 2 A, started from malic acid and 1,2,4-triacetoxybenzene (**7**) and afforded isoflavy-



Scheme 1. A) Proposed biosynthetic pathway leading to santalin Y. B) A modification of the proposal involving excited-state intramolecular proton transfer and a concerted cycloaddition.



Scheme 2. A) Synthesis of isoflavylium salt **8** and anhydrobase **5**. B) Synthesis of benzylstyrene **2**. TBDPS = *tert*-butyldiphenylsilyl, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

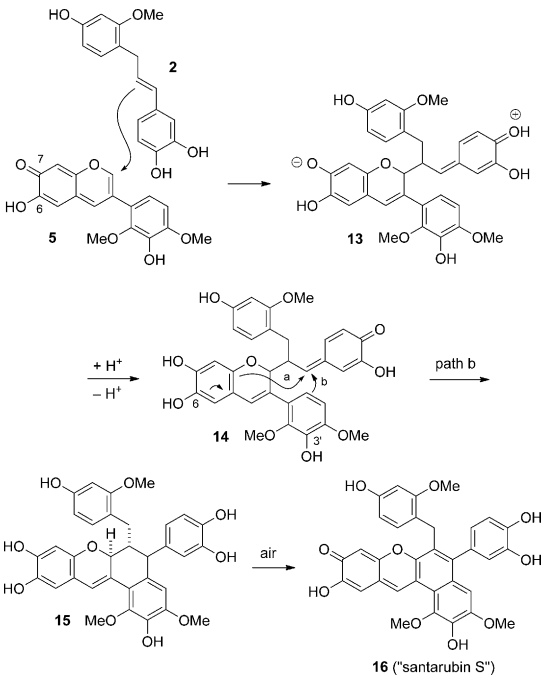
lium perchlorate **8** and anhydrobase **5** in 7 and 8 steps, respectively.

The requisite benzylstyrene **2** was prepared by olefin cross-metathesis, as shown in Scheme 2 B. Monoallylation of resorcinol, followed by protection of the remaining phenolic hydroxy group as a silyl ether gave **9**, which underwent a Lewis acid catalyzed Claisen rearrangement,[10] methylation, and deprotection to yield allyl resorcinol **10**. Conversely, protection of the catechol **11**, followed by Wittig olefination, afforded styrene **12** as an inseparable mixture of the *E* and *Z* isomers (1.7:1). Cross-metathesis of **10** and **12**, followed by global deprotection, then gave *E*-configured benzylstyrene **2** as a single diastereomer.

With building blocks **5, 8**, and **2** in hand, we first investigated the possibility of synthesizing santalin Y by photochemically triggered ESIPT,[11] followed by 1,3-dipolar cycloaddition, as outlined in Scheme 1 B. However, despite an extensive screening of solvents, light sources, and additives, santalin Y could never be isolated and this approach was abandoned (see the Supporting Information).

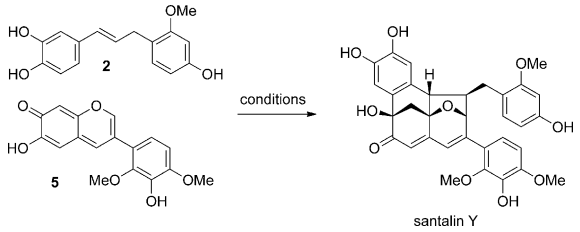
Since our photochemical strategy proved unsuccessful, we began to investigate thermal conditions. When benzylstyrene **2** was exposed to isoflavylium perchlorate **8**, which corresponds to **1** in Nohara's proposal,[7] rapid decomposition of **2** was observed. This decomposition was attributed to the acidity of **8**, which might initiate polymerization of the styrene. Consequently, the moderately basic anhydrobase **5**, obtained by deprotonation of **8**, was heated in the presence of benzylstyrene **2** in a variety of solvents. Although santalin Y was never found under these conditions, we often detected the benzoxanthenone **16** as a product (Scheme 3, see the Supporting Information). The addition of Lewis and Brønsted acids gave various amounts of **16**, but no santalin Y. The formation of **16** presumably involves a nucleophilic attack of **2** on anhydrobase **5**. The resulting adduct, shown here without considering the stereochemistry, could then undergo proton transfer to afford **14**. Deprotonation of this intermediate and cyclization along pathway b (whereas pathway a would have led to santalin Y), followed by oxidation of the labile product **15** by ambient air then yields compound **16**. Benzoxanthenone **16** has not been described as a genuine natural product, but closely resembles santarubin A and B.[6a] If it were to be isolated from natural materials we propose to call this brightly colored compound "santarubin S".

Contemplating the mechanism shown in Scheme 3, we realized that we had to find a way to bias the cyclization of intermediate **14** toward path a. We reasoned that this could be achieved with a bifunctional organocatalyst[12] that could activate the anhydrobase **5** toward nucleophilic attack by hydrogen bonding to the carbonyl function at C7 and subsequently deprotonate the phenolic hydroxy group at C6. Indeed, when the racemic Takemoto catalyst **17**[12k,13] was employed in THF solution, we were able to detect the formation of santalin Y for the first time (Table 1, entry 1). This reaction, however, proved to be difficult to reproduce and the solubility of our starting materials in THF was low. We, therefore, screened for better solvents that could also serve as hydrogen-bond donors, mediate proton transfers, and stabilize ionic intermediates. Amongst these, trifluoroethanol (TFE) turned out to be the most suitable. When an equimolar mixture of **2** and **5** in TFE solution was exposed to 20 mol% of **17** at −20 °C, santalin Y was formed in 45% yield, as determined by NMR spectroscopy (entry 2). The use of a stoichiometric amount of catalyst **17** did not significantly



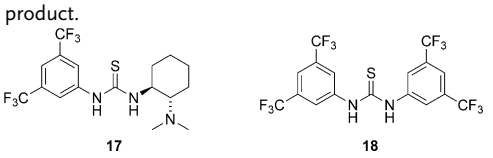
Scheme 3. Formation of the benzoxanthenone **16** ("santarubin S") by an unintended cyclization.

Table 1: Optimization of the reaction conditions.



Entry[a]	Additives (equiv)	Solvent	Conc. [M]	*T* [°C]	Yield [%][b]
1	**17** (0.2)	THF	0.015	−20 °C	0–20
2	**17** (0.2)	TFE	0.015	−20 °C	45
3	**18** (0.2)	TFE	0.015	−20 °C	0
4	**17** (1)	TFE	0.015	−20 °C	43
5	**17** (0.2)	TFE	0.03	−20 °C	51
6	**17** (0.2)/Et_3N (1)	TFE	0.015	−20 °C	64
7	**17** (0.2)/Et_3N (1)	TFE	0.015	RT	39
8	Et_3N (1)	TFE	0.015	RT	40
9	Et_3N (0.2)	TFE	0.015	−20 °C	52
10	Et_3N (1)	TFE	0.06	−20 °C	81 (67)[c]

[a] Conditions: compound **5** (1 equiv), compound **2** (1 equiv), 48 h, under Ar. [b] Yield calculated by NMR spectroscopy. [c] Yield of isolated product.



change the outcome of the reaction (entry 4), while increasing the concentration was beneficial (entry 5). Schreiner's organocatalyst **18**[12l,14] was ineffective, thus highlighting the importance of the basic functionality of **17** (entry 3). The addition of an external base, such as Et_3N, further increased the yield (entry 6). However, when the reagents were added at room temperature instead of −20 °C, we observed a drop in the yield (entry 7).

We next omitted the organocatalyst **17** and ran the reaction in TFE solution and in the presence of various amounts of Et_3N. Surprisingly, these conditions also provided santalin Y in decent yields (entries 8 and 9). Apparently, the solvent TFE and the base Et_3N can substitute for the bifunctional catalyst. Finally, after considerable experimentation (see the Supporting Information), we arrived at the optimal conditions for the synthesis of santalin Y. Exposure of **2** and **5** in TFE at their solubility limit ($c = 0.06$ M) to Et_3N at −20 °C, followed by warming to room temperature and stirring for 12 h, gave the racemic natural product in 81 % yield, as determined by NMR spectroscopy, and 67 % yield of the isolated product (Table 1, entry 10). Compound **16** was not observed under these optimized conditions.

The spectroscopic data of our synthetic santalin Y fully matched those reported for the natural product. This was further confirmed by an independent X-ray structure analysis of synthetic santalin Y as its acetonitrile solvate (Figure 1 and see the Supporting Information).

Insight into the mechanism of our key reaction was obtained through quantum chemical computations.[15] First, we established that the 1,3-dipole **6** is only 7–10 kcal mol^{-1} higher in energy than anhydrobase **5**. The energy barrier for conversion of **5** into **6** by thermal intramolecular proton transfer was predicted to be 10–12 kcal mol^{-1} (see the Supporting Information). It is, therefore, conceivable that **6** is formed in sufficient concentrations under thermal conditions. Second, once it is formed, we found a favorable pathway for the cycloaddition of **6** to benzylstyrene **2** (Figure 3). The energy barrier of this reaction was estimated to be approximately 20 kcal mol^{-1} (free energies with M06-2X/6-31G(d), although the absolute barrier height varied with the level of theory used; see the Supporting Information). This is compatible with our optimized reaction conditions (−20 °C to RT). The energy of the transition-state structure **TS-1**, which leads to **4**, was found to be lower than that of **TS-2**, which would afford **19**, a diastereomer of **4**, by 0.3–3.0 kcal mol^{-1}, depending on the level of theory employed (see the Supporting Information). Note that the dipole and dipolarophile portions of this transition-state structure interact through π-stacking and hydrogen-bonding interactions.[16] Although bond formation in all of the transition-state structures examined occurs asynchronously, no intermediates expected for stepwise pathways were found. We therefore favor a concerted cycloaddition mechanism.[17a] The role of the polar and comparatively acidic solvent TFE in combination with the base Et_3N in our optimal conditions could lie in facilitating the proton transfers that equilibrate **5** with **6**.

In conclusion, we have developed a concise, diastereoselective and highly convergent synthesis of santalin Y. This complex, yet racemic, natural product was synthesized in

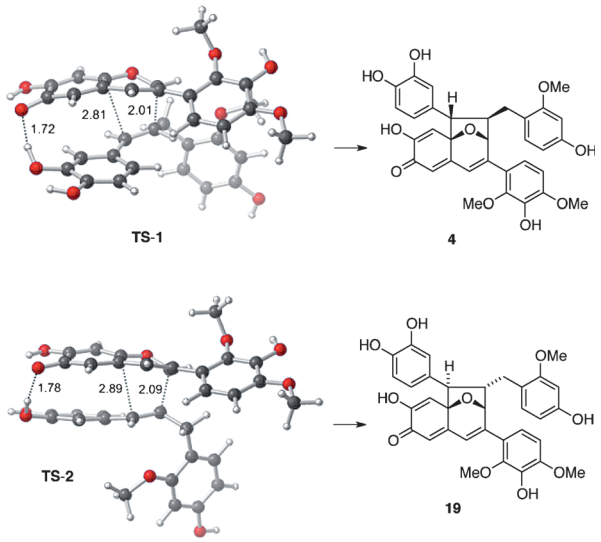


Figure 3. Computed transition-state structures (M06-2X/6-31G(d); selected distances in [Å]). Top: Transition-state structure **TS-1** for the formation of **4**. Bottom: Transition-state structure **TS-2** for the formation of the unobserved diastereomer **19**. At this level of theory, **TS-1** is predicted to be 1.4 kcal mol^{-1} lower in energy than **TS-2**.

7 steps (longest linear sequence) and in 8 % overall yield from readily available starting materials. Our results indicate that an isoflavylium (**1**) and a benzylstyrene (**2**), which have not yet been isolated as genuine natural products, are biosynthetic progenitors of santalin Y. We also provide evidence that a concerted cycloaddition is involved, although a stepwise mechanism cannot be entirely ruled out. Santalin S (**16**) is proposed as a natural product. Our results demonstrate, once again, that enzymes are not always necessary to promote reactions that lead to complex natural products.[17] It would be difficult to conceive of a non-biomimetic synthetic strategy that could deliver santalin Y in such an expedient way.

Experimental Section

Triethylamine (5 μL, 0.0356 mmol, 1 equiv) was added to a stirred solution of anhydrobase **5** (14 mg, 0.0445 mmol, 1.2 equiv) and benzylstyrene **2** (9.7 mg, 0.0356 mmol, 1 equiv) in TFE (0.6 mL) at −20 °C. The reaction mixture was allowed to reach room temperature and was stirred for 12 h. Then, the reaction mixture was concentrated in vacuo. The crude product was purified twice by preparative TLC (CH_2Cl_2/MeOH 10:1) and afforded santalin Y (15.5 mg, 67 %) as a yellow powder. Santalin Y could be recrystallized in acetonitrile to give yellow crystals. $R_f = 0.38$ (CH_2Cl_2/MeOH 9:1). UV (MeCN): $\lambda_{max} = 357$ nm. IR (ATR): $\tilde{\nu} = 3271$ (m), 2925 (s), 2854 (s), 1733 (w), 1666 (m), 1596 (m), 1508 (m), 1462 (m), 1381 (w), 1278 (s), 1243 (m), 1176 (s), 1131 (s), 1024 (s), 1005 cm^{-1} (m). HRMS (ESI): calcd for $C_{33}H_{31}O_{10}^+$ $[M+H]^+$: 587.1912, found: 587.1918. ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta = 9.21$ (s, 1 H), 8.88 (s,1 H), 8.78 (s, 1 H), 8.66 (s, 1 H), 6.91 (d, $J = 8.1$ Hz, 1 H), 6.81 (s, 1 H), 6.42 (d, $J = 8.9$ Hz, 1 H), 6.50 (d, $J = 0.8$ Hz, 1 H), 6.36 (s, 1 H), 6.27 (d, $J = 2.3$ Hz, 1 H), 6.18 (dd, $J = 8.0$, 2.3 Hz, 1 H), 6.07 (d, $J = 8.8$ Hz), 5.82 (s, 1 H), 5.62 (d, $J = 0.6$ Hz, 1 H), 4.84 (s, 1 H), 3.77 (s, 3 H), 3.66 (s, 3 H), 3.56 (s, 3 H), 3.30 (m, 1 H), 3.00 (dd, $J = 13.8$, 4.0 Hz, 1 H), 2.67 (dd, $J = 13.8$, 10.3 Hz, 1 H), 2.62–2.47 (ABq, $J = 10.7$ Hz, 2 H), 2.46 ppm (m, 1 H). ^{13}C NMR (150 MHz, [D$_6$]DMSO): $\delta = 198.4$, 157.9, 157.4, 154.9, 152.9, 149.6, 146.2, 145.5, 143.7, 139.5, 130.6, 128.8, 124.5, 121.5, 120.8, 119.8, 118.0, 117.9, 113.8,

112.3, 107.0, 106.6, 98.9, 83.2, 80.9, 78.0, 59.8, 55.8, 55.0, 54.9, 50.6, 46.3, 36.4 ppm.

Keywords: biomimetic synthesis · dipolar cycloaddition · polyphenols · racemic natural products · total synthesis

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[15] All calculations were carried using GAUSSIAN 09 (Gaussian 09 (Revision B.01), M. J. Frisch, et al., Wallingford CT, **2009**). Several density functional theory methods were used (see the Supporting Information for details); SMD(trifluoroethanol)-M06-2X/6-311++G(2d,p)//M06-2X/6-31G(d) results (M06-2X: Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241, SMD: A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396) are described in the text. Calculations on small model systems and the reactions promoted by the Takemota catalyst are described in the Supporting Information.
[16] Theozyme (D. J. Tantillo, J. Chen, K. N. Houk, *Curr. Opin. Chem. Biol.* **1998**, *2*, 743–750) calculations were performed with one TFE molecule hydrogen bonded to various oxygen atoms of the transition-state structure. These calculations, despite their shortcomings, indicate that specific hydrogen bonding, especially hydrogen-bond donation to the oxo oxygen atom of **6**, can lead to barrier lowering.
[17] a) S. C. Wang, D. J. Tantillo, *J. Org. Chem.* **2008**, *73*, 1516–1523; b) P. P. Painter, R. P. Pemberton, B. M. Wong, K. C. Ho, D. J. Tantillo, *J. Org. Chem.* **2014**, *79*, 432–435; c) E. H. Krenske, A. Patel, K. N. Houk, *J. Am. Chem. Soc.* **2013**, *135*, 17638–17642.

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