*Natural Products Synthesis*

# Biomimetic Total Synthesis of Gambogin and Rate Acceleration of Pericyclic Reactions in Aqueous Media**

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Gambogin (**1**, Scheme 1) has an unusual molecular architecture and exhibits cytotoxic properties against the Hela and HEL cell lines (MIC: 6.25 and 3.13 $\mu g\,mL^{-1}$, respectively).[1] Isolated from the gamboge resin of *Garcina hamburyi* in 1996, this naturally occurring substance provides an intriguing synthetic challenge and an opportunity for the development of new synthetic technology and biological tools. Herein we report a biomimetic[2] total synthesis of gambogin[3] and the observation of dramatic rate accelerations of the Claisen rearrangement and the Claisen/Diels–Alder cascade reaction[4] in protic solvents, most notably in water.

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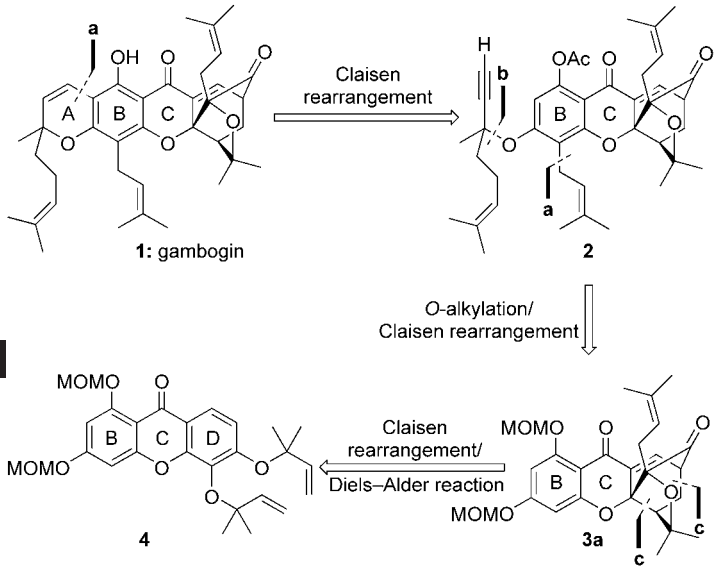
[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. We thank Robert Reuter (Novartis) for the biological evaluations of gambogin and its analogues. Financial support for this work was provided by grants from the National Institutes of Health (USA) and the Skaggs Institute for Chemical Biology, and a fellowship from the Skaggs Institute for Research (to H.X.).

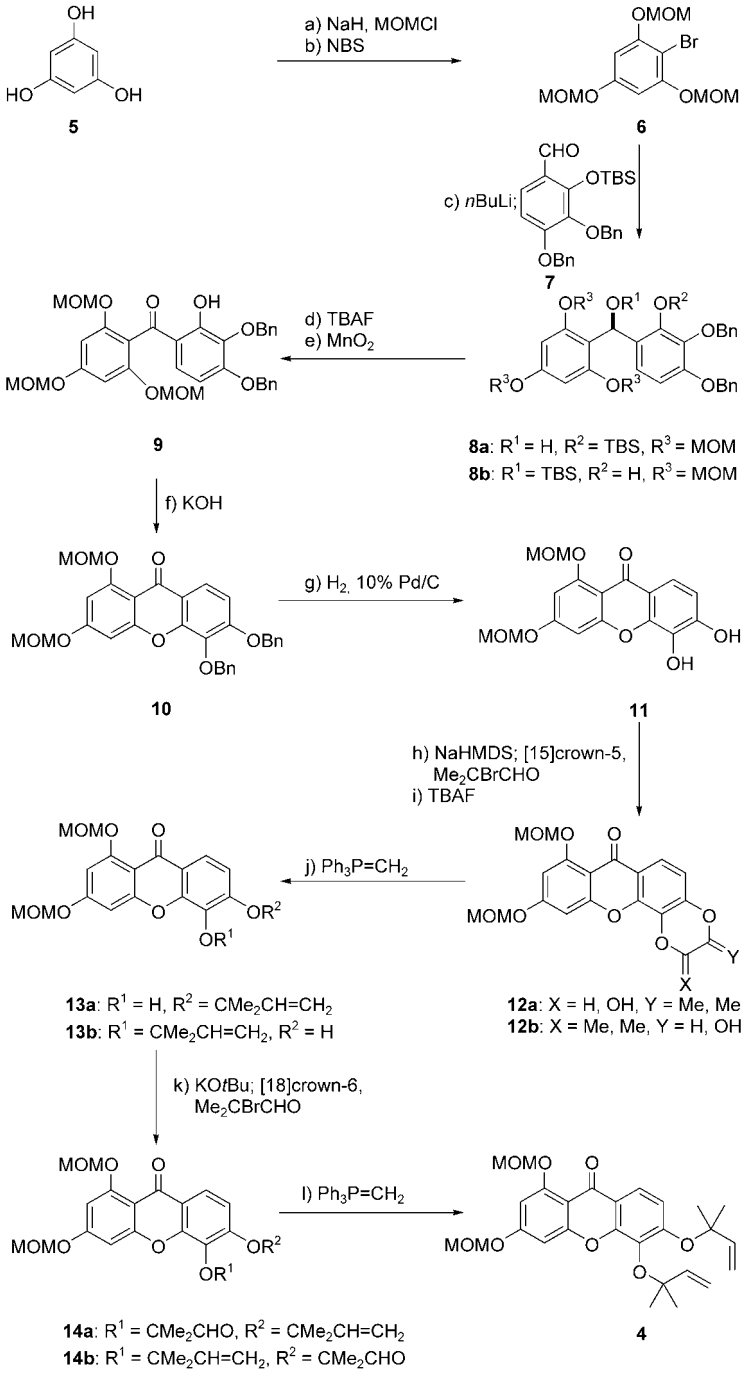
Our retrosynthetic plan for the molecule of gambogin (**1**), whose resemblance to forbesione and lateriflorone[5] influenced our thinking, is shown in Scheme 1. Thus, applying a retro-Claisen rearrangement[6] on ring A (benzopyran ring, mixture of diastereomers) unraveled the acetylenic benzenoid compound **2**, which could be derived from **3a** through *O*-alkylation and, yet again, a Claisen rearrangement. Finally, the cagelike trioxatetracyclo[7.4.1.0$^{2,7}$.0$^{2,11}$]tetradecane system[7] was dismantled as previously[5] to the BCD tricycle **4**, whose construction from readily available starting materials was reasonably anticipated. Most significantly, the synthetic plan that emerged from this analysis offered us the opportunity to investigate the possibility of accelerating pericyclic reactions such as the Claisen and Diels–Alder reactions beyond their previously defined boundaries.




***Scheme 1.*** Retrosynthetic analysis of gambogin (1): a) Claisen rearrangement; b) *O*-alkylation; c) Diels–Alder reaction.

The required intermediate **4** was synthesized as summarized in Scheme 2. Phloroglucinol (**5**) was protected with three MOM groups, and the resulting compound was brominated with NBS to afford intermediate **6** in 62% overall yield. Lithiation of **6**, followed by trapping of the generated anion with fully functionalized benzaldehyde **7**[5b,c] in diethyl ether generated bis-aromatic system **8a** in 85% yield. However, when THF was used as the solvent in large-scale operations for solubility considerations, a spontaneous silyl group migration[8] took place, affording **8b** cleanly and in 85% yield. Desilylation of **8a** or **8b** with TBAF and subsequent oxidation with $MnO_2$ furnished ketone **9** in 68% overall yield. Ketone **9** was heated at reflux in a solution of KOH (EtOH/$H_2O$) which induced an intramolecular conjugate addition/elimination[9] to afford tricyclic system **10**. Subsequent hydrogenolysis of the two benzyl groups of **10** in THF led to the highly oxygenated xanthone **11** in 76% overall yield. Lactolization of the catechol system of **11** through our previously reported method[5b,c] (KO*t*Bu, [18]crown-6) failed to produce the desired lactols (**12a**/**12b**) in high yield. The procedure was

  DOI: 10.1002/anie.200462211 



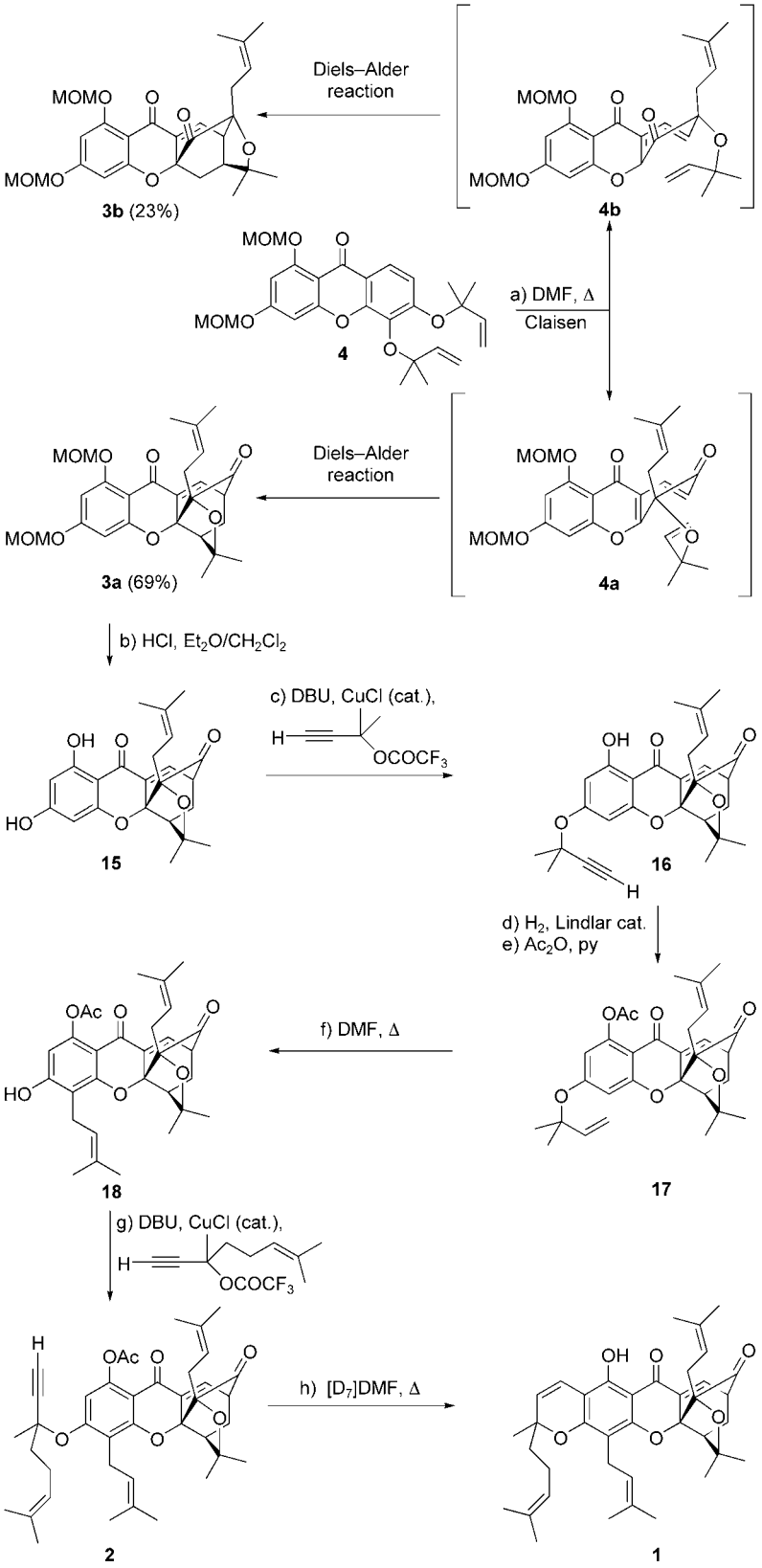

***Scheme 2.*** Synthesis of advanced intermediate **4**: a) NaH (4.0 equiv), MOMCl (3.5 equiv), DMF, 0→25 °C, 2 h, 65%; b) NBS (1.05 equiv), $CH_2Cl_2$, 25 °C, 1 h, 95%; c) *n*BuLi (1.08 equiv), THF or diethyl ether, −78 °C, 2 h; then **7** (1.0 equiv), −78→0 °C, 0.5 h, 85%; d) TBAF (1.1 equiv), THF, 0 °C, 15 min, 90%; e) $MnO_2$ (10.0 equiv), $CH_2Cl_2$, 25 °C, 12 h, 75%; f) NaOH (5.0 equiv), EtOH, 90 °C, 24 h, 80%; g) Pd/C (10 wt%), $H_2$ (1 atm), THF, 25 °C, 2 h, 95%; h) NaHMDS (2.2 equiv), THF, 0 °C, 30 min; then concentrated and suspended in MeCN; then [15]crown-5 (2.2 equiv), 15 min, bromoisobutyraldehyde (4.0 equiv), 0→25 °C, 30 min; i) TBAF (1.2 equiv), THF, 0 °C, 15 min, 71% over two steps; j) $CH_3P^+Ph_3Br^-$ (3.5 equiv), NaHMDS (3.5 equiv), THF, 0 °C, 1 h; then **12** was added to the generated ylide, 0→25 °C, 0.5 h, 80%; k) KO*t*Bu (1.2 equiv), THF, 0 °C, 30 min; then concentrated and suspended in MeCN; then [18]crown-6 (1.2 equiv), 15 min, bromoisobutyraldehyde (4.0 equiv), 0→25 °C, 2 h, 85%; l) $CH_3P^+Ph_3Br^-$ (1.5 equiv), NaHMDS (1.5 equiv), THF, 0 °C, 1 h; then **14** was added to the generated ylide, 0→25 °C, 0.5 h, 87%. MOM = methoxymethyl, DMF = *N*,*N*-dimethylformamide, NBS = *N*-bromosuccinimide, TBAF = tetra-*n*-butylammonium fluoride, HMDS = hexamethyldisilazane.

modified so as to include NaHMDS and [15]crown-5 instead. The disodium salt of **11**, generated by addition of NaHMDS, was first suspended and then completely dissolved in acetonitrile after addition of [15]crown-5 and sonication. Treatment of this solution with freshly prepared bromoisobutyraldehyde[10] afforded a mixture of regioisomeric TMS-protected lactols (≈1:1) at 0 °C in only 20 min. The unexpected silylation of the lactol moiety might be rationalized by envisioning an intermolecular lactol anion attack of the hexamethyldisilazane generated in situ owing to the enhanced nucleophilicity of the former. Desilylation (TBAF) followed by reaction of the resulting lactols (**12a**/**12b**) with methylene phosphorane provided regioisomeric olefins **13a** and **13b** (≈1:1, 57% over three steps). The original KO*t*Bu/[18]crown-6 protocol proved successful in the second alkylation. Thus, a Wittig olefination sequence converted **13a**/**13b**, via aldehydes **14a**/**14b**, into the desired diolefin **4** in 74% overall yield.

Upon heating in DMF at 120 °C, the xanthone derivative **4** smoothly underwent the expected Claisen/Diels–Alder cascade sequence through the presumed intermediates **4a** and **4b** (Scheme 3) to furnish **3a** and **3b** in 69% and 23% yield, respectively. The structural assignments of these compounds were supported by NOE studies. Removal of the MOM groups from the desired isomer **3a** was smoothly effected through the action of HCl (1.0 M in $CH_2Cl_2$/$Et_2O$ (1:1)), which generated catechol **15** in 85% yield. As one of the phenolic groups in **15** was deactivated owing to internal hydrogen bonding, we were able to effect selective monopropargylation of the other with $CH{\equiv}CC(Me)_2OCOCF_3$ in the presence of DBU and CuCl[11] in 60% yield (85% based on 70% conversion). Further selective reduction and acetylation furnished olefin **17**, whose Claisen rearrangement proceeded regioselectively and in 69% overall yield from **16**, to afford the prenylated aromatic system **18** as a single isomer. A second propargylation, this time with CH≡CC(Me)-$[CH_2CH_2CH{=}CC(Me)_2]OCOCF_3$,[12] was applied to convert **18** into **2** cleanly, albeit in relatively low conversion as a result of the steric hindrance encountered in the transition state (26% yield; 88% based on 30% conversion). Finally, heating of propargyl ether **2** in [$D_7$]DMF at 140 °C led directly to gambogin (**1**) as a yellow foam in 65% yield.[13] The high temperature employed in the last operation was apparently sufficient encouragement for the acetate group to depart. Three gambogin analogues (**20a**–**c**) were synthesized through the same strategy (Scheme 4).

The conversion of aryl ether **17** into the prenylated aromatic system **18** provided a good opportunity to investigate solvent effects on the rate of the Claisen rearrangement. Previous work in this field,[14] including ours,[6a] was suggestive of the requirement of heating up to 180 °C in aprotic

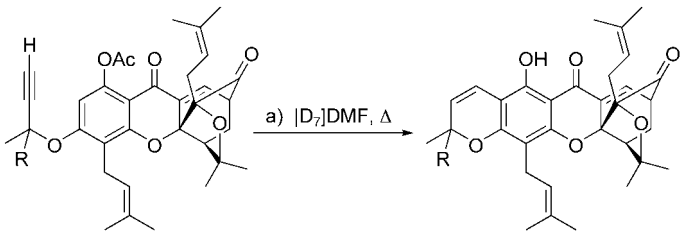



solvents such as DMF or *N*,*N*-diethylaniline, although temperatures as low as 60 °C were successfully employed by Grieco and co-workers[14f] for a Claisen rearrangement of an aliphatic system. The theoretical studies of Jorgensen and Severance,[15] in particular, were encouraging to us, for they pointed to a favorable hydrogen-bonding effect in protic solvents on the rate of pericyclic reactions such as the one under investigation. Table 1 summarizes the results of this study in which various solvents and temperatures were employed. As expected, in [$D_6$]benzene, there was no detectable reaction of **17** after 4 h at 100 °C, nor did the substrate react in ethanol or trifluoroethanol at 25 °C after the same period of time. In [$D_7$]DMF, however, we began to observe conversion of **17** into **18** through the Claisen rearrangement at 50 °C (4.5 h, 25 % conversion), whereas at 100 °C, the reaction was complete within 0.5 h. The same accelerating effect was noticed in methanol at 50 °C (4.5 h, 50 % conversion) and 100 °C (0.5 h, 100 % conversion). The addition of water to the latter solvent ($MeOH/H_2O = 2:1$) resulted in an even faster reaction (50 °C: 3.5 h, 100 % conversion or 100 °C: 0.25 h, 100 % conversion), whereas an increase in the water content of the solvent mixture to 1:1 provided similar rate acceleration (50 °C: 2.5 h, 100 % conversion or 100 °C: 0.25 h, 100 % conversion). Further addition of water was detrimental owing to precipitation of the substrate. The highest rate acceleration, however, was observed in trifluoroethanol/$H_2O$ (1:1) (25 °C: 75 h, 100 % conversion or 40 °C: 65 h, 100 % conversion) and ethanol/$H_2O$ (1:1) (25 °C: 72 h, 100 % conversion or 40 °C: 60 h, 100 % conversion). The ability to carry out this type of Claisen rearrangement at ambient temperature is unprecedented and is expected to expand the scope of this process to include otherwise fragile substrates and/or products.

Encouraged by these results, we proceeded to explore the effect of the same solvents on the Claisen/Diels–Alder cascade sequence involved in the conversion of **4** into **3a** (and **3b**, see Scheme 3). Table 2 exhibits the findings of this study. Thus, in [$D_6$]benzene, there was no reaction at 100 °C after 4 h, and no detectable reactions occurred in ethanol, trifluoroethanol or [$D_7$]DMF at 65 °C after 4 h. In [$D_7$]DMF at 100 °C,

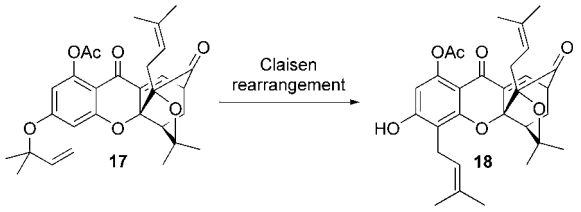
***Scheme 3.*** Total synthesis of gambogin (**1**): a) DMF, 120 °C, 1 h, **3a** (69 %) and **3b** (23 %); b) HCl (1.0 M) in $Et_2O/CH_2Cl_2$ (1:1), 25 °C, 24 h, 85 %; c) propargyl alcohol (1.4 equiv), DBU (1.4 equiv), TFAA (1.4 equiv), MeCN, 0 °C, 30 min; DBU (1.5 equiv), CuCl (0.1 % equiv), 15 min; then TFA propargyl ester, 0 °C, 5 h, 60 % (85 % based on 70 % conversion); d) Lindlar catalyst (10 wt %), $H_2$ (1 atm), EtOAc (contaminated with 0.02 % quinoline), 25 °C, 1 h, 95 %; e) $Ac_2O$ (10.0 equiv), py (10.0 equiv), 4-DMAP (1.0 equiv), $CH_2Cl_2$, 25 °C, 8 h, 85 %; f) DMF, 120 °C, 0.5 h, 85 %; g) propargyl alcohol (1.4 equiv), DBU (1.4 equiv), TFAA (1.4 equiv), MeCN, 0 °C, 30 min; DBU (1.5 equiv), CuCl (0.1 % equiv), 15 min; then TFA propargyl ester, 0 °C, 5 h, 26 % (88 % based on 30 % conversion); h) [$D_7$]DMF, 140 °C, 2 h, 65 %. DBU = 1,8-diazabicyclo[5, 4, 0]undec-7-ene, TFAA = trifluoracetic anhydride, py = pyridine, 4-DMAP = 4-dimethylaminopyridine.




***Scheme 4.*** Synthesis of analogues **20a–c** of gambogin: a) [$D_7$]DMF, 140 °C, 2 h, 65 %.

***Table 1:*** Solvent effects on the rate of the Claisen rearrangement of **17** into **18**.[a]



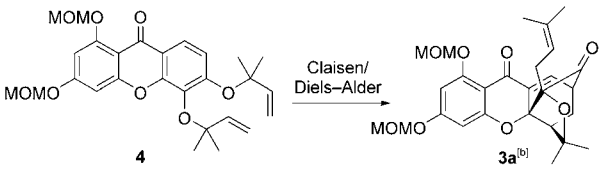

| Entry | Solvent | *T* [°C] | *t* [h] | Conversion [%] |
|---|---|---|---|---|
| 1 | [$D_6$]benzene | 100 | 4 | 0 |
| 2 | EtOH | 25 | 4 | 0 |
| 3 | TFE[b] | 25 | 4 | 0 |
| 4 | [$D_7$]DMF | 50 | 4.5 | 25 |
| 5 | [$D_7$]DMF | 100 | 0.5 | 100 |
| 6 | MeOH | 50 | 4.5 | 50 |
| 7 | MeOH | 100 | 0.5 | 100 |
| 8 | MeOH/$H_2O$ (2:1) | 50 | 3.5 | 100 |
| 9 | MeOH/$H_2O$ (2:1) | 100 | 0.25 | 100 |
| 10 | MeOH/$H_2O$ (1:1) | 50 | 2.5 | 100 |
| 11 | MeOH/$H_2O$ (1:1) | 100 | 0.25 | 100 |
| 12 | TFE/$H_2O$ (1:1) | 25 | 75 | 100 |
| 13 | TFE/$H_2O$ (1:1) | 40 | 65 | 100 |
| 14 | EtOH/$H_2O$ (1:1) | 25 | 72 | 100 |
| 15 | EtOH/$H_2O$ (1:1) | 40 | 60 | 100 |

[a] The reactions were carried out on a 0.1–1.0-mmol scale and monitored by disappearance of starting material by TLC and $^1$H NMR spectroscopy. [b] TFE = trifluoroethanol.

however, the reaction started to proceed (2 h, 75 % conversion). In methanol, although there was no reaction at 65 °C after 4 h, the sequence was complete after only 1 h at 100 °C. An increase in the amount of water in the methanolic solvent (MeOH/$H_2O$ 2:1→1:1→1:2) caused a rather dramatic effect in rate acceleration (100 % conversion at 100 °C after 0.5–1 h, Table 2, entries 9, 11, and 15, or 100 % conversion at 65 °C after 3.5–4.5 h, Table 2, entries 8, 10, and 14). This remarkable effect was also observed more or less unchanged in ethanol/water (1:1) and trifluoroethanol/water (1:1) mixtures (Table 2, entries 12 and 13).

The explanation for the observed rate acceleration of both the Claisen rearrangement and the Diels–Alder reaction constituting the cascade sequence in the conversion of **4** into **3a** can be found in previous theoretical as well as experimental work.[14,16] For the Claisen rearrangement, the model[14g] shown in Figure 1, as developed by Jorgensen and

***Table 2:*** Solvent effects on the rate of the Claisen/Diels–Alder cascade of **4** into **3a**.[a]




| Entry | Solvent | *T* [°C] | *t* [h] | Conversion [%] |
|---|---|---|---|---|
| 1 | [$D_6$]Benzene | 100 | 4 | 0 |
| 2 | EtOH | 65 | 4 | 0 |
| 3 | TFE | 65 | 4 | 0 |
| 4 | [$D_7$]DMF | 65 | 4 | 0 |
| 5 | [$D_7$]DMF | 100 | 2.0 | 75 |
| 6 | MeOH | 65 | 4 | 0 |
| 7 | MeOH | 100 | 1.0 | 100 |
| 8 | MeOH/$H_2O$ (2:1) | 65 | 4.5 | 100 |
| 9 | MeOH/$H_2O$ (2:1) | 100 | 1.0 | 100 |
| 10 | MeOH/$H_2O$ (1:1) | 65 | 4.0 | 100 |
| 11 | MeOH/$H_2O$ (1:1) | 100 | 0.5 | 100 |
| 12 | TFE/$H_2O$ (1:1) | 65 | 4.0 | 100 |
| 13 | EtOH/$H_2O$ (1:1) | 65 | 4.0 | 100 |
| 14 | MeOH/$H_2O$ (1:2) | 65 | 3.5 | 100 |
| 15 | MeOH/$H_2O$ (1:2) | 100 | 0.5 | 100 |

[a] The reactions were carried out on a 0.1–1.0-mmol scale and monitored by disappearance of starting material by TLC and $^1$H NMR spectroscopy. [b] The ratio of the two products **3a**:**3b** (see Scheme 3) stayed constant (≈3:1) during the course of the reactions.

Severance[15] based on Monte Carlo calculations, postulates one hydrogen bond from the solvent to one of the lone pairs of electrons of the ethereal oxygen atom in the ground state **4** and two hydrogen bonds from two solvent molecules to both lone pairs of electrons of the oxygen atom in the transition state **4-TS**, by virtue of the distortion of conjugation as the reaction begins to occur, a condition that results in catalysis. This bifurcated-hydrogen-bond hypothesis has found corroboration in the X-ray crystal structures of chorismate mutase isolated from *Bacillus subtilis* (BsCM)[17] and *Escherichia coli* (EcCM),[18] the enzyme that catalyzes the Claisen rearrangement[19] of the chorismate anion to the prephenate anion. Thus, whereas the polar aprotic solvent DMF can only accelerate the nonsynchromic, semi-zwitterionic[20] Claisen rearrangement by stabilizing its polar transition state, the protic solvents, because of their hydrogen-bond-donor abilities[21] (most notably water), are able to provide additional stabilization of the transition state and thus promote the dramatic acceleration effects observed.[22] It was interesting to note that a further increase in the water content in these alcoholic solvents resulted in the precipitation of the substrate and shut-down of the reaction, presumably as a result of the insufficient solvation that accompanied the observed precipitation of the reacting substrate. The concurrent acceleration of the Diels–Alder component of the cascade is due, as explained by Breslow and co-workers,[16,23] to the hydrophobic effect[24] and the unique internal pressure of water rather than simple polarity or hydrogen-bonding phenomena. It was interesting to note that at no temperature in any solvent system could we detect any of the postulated intermediate dienone **22**, leading us to conclude that the Diels–Alder[25]

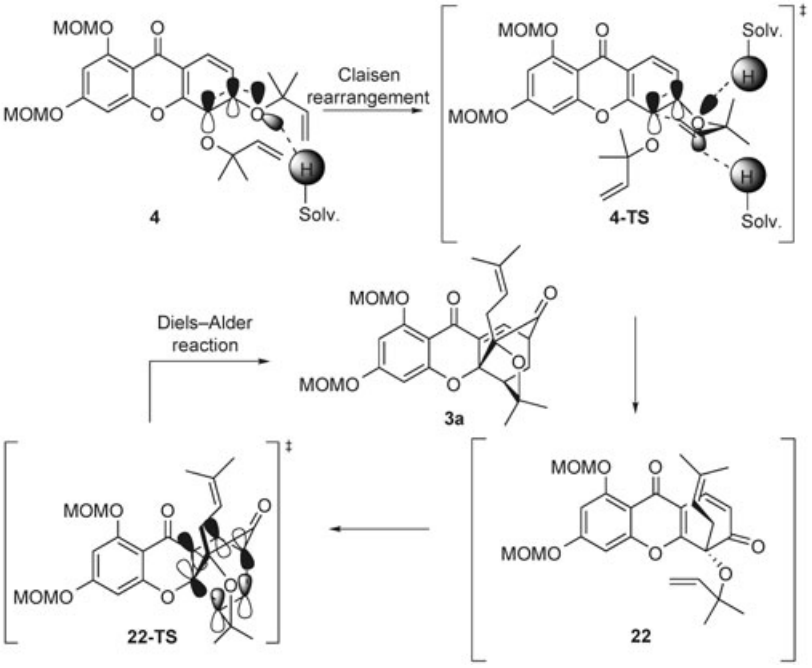



***Figure 1.*** Molecular-orbital rationale for the acceleration of the Claisen/Diels–Alder cascade reaction (**4**→**3a**) by protic solvents.

intramolecular collapse was the faster of the two pericyclic reactions involved in this cascade. To the best of our knowledge, this is the first example of a Claisen/Diels–Alder cascade sequence accelerated by water.

The synthesized compounds **20a–c**, except for **20a**, which are diastereomeric mixtures, like gambogin **1** itself, were tested for their cytotoxicity against human epidermoid cancer cell line KB-31 and its taxol-resistant mutant cell line KB-8511. The results are shown in Table 3. Both the methyl- and isopentyl-substituted analogues **20a** and **20c** exhibited

***Table 3:*** Cytotoxicity of gambogin (**1**) and its analogues (**20a–c**).[a]

| Entry | Compound | $IC_{50}$ [μM] | |
|---|---|---|---|
| | | KB-31 | KB-8511 |
| 1 | **1** | 9.35 | >10 |
| 2 | **20a** | 8.41 | >10 |
| 3 | **20b** | >10 | >10 |
| 4 | **20c** | 6.01 | >10 |

[a] The antiproliferative effects of the tested compounds were assessed in human epidermoid cancer cell lines: the parent cell line (KB-31) and the taxol-resistant (due to Pgp-overexpression) cell line (KB-8511).

slightly higher potencies than the natural compound **1** against KB-31, while the ethyl derivative **20b** was less active. All compounds, including gambogin itself, failed to exhibit significant cytotoxicity against the taxol-resistant mutant cell line KB-8511 at concentrations below 10 μM. The chemistry described herein may provide entries to biologically active molecules of the gambogin type and stimulate further studies in the reaction process development.

Received: October 5, 2004

**Keywords:** Claisen rearrangement · Diels–Alder reaction · natural products · rate acceleration · total synthesis

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