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A Unique Skeletal Rearrangement of a Bicyclo[3.3.1]nonanetrione to a Tetrahydroquinolin-2(1*H*)-one System

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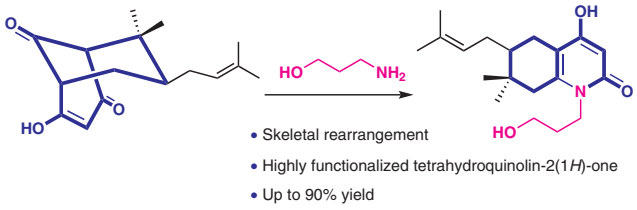

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Abstract The unexpected formation of a 4-hydroxytetrahydroquinolin-2(1*H*)-one from a bicyclo[3.3.1]nonanetrione system and an amino alcohol in the presence of TsOH is reported. The mechanism of this transformation was studied by DFT calculations. The reaction provides an entry to the synthesis of highly functionalized 4-hydroxytetrahydroquinolin-2(1*H*)-ones.

Key words polyprenylated acylphloroglucinols, skeletal rearrangement, tetrahydroquinolinones, density functional theory, bicyclononanetriones, tetrahydroquinolinones

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a family of natural products isolated from the Guttiferae (Clusiaceae) family of plants, which feature a variety of complex structural motifs such as a highly oxygenated and an unusual bicyclo[3.3.1]nonanetrione skeleton bearing prenyl or geranyl side chains (Figure 1).[1] Well over 150 PPAPs have been isolated, with properties ranging from antiviral to anticancer activities. The diverse biological activities of PPAPs, as well as their complex and intriguing structures, make them attractive targets for total synthesis, but a global model correlating the biological function of PPAPs with their structural type or substitution pattern is lacking.[2] With these challenges in mind, we sought to develop more analogues of PPAPs so that we might elucidate the structure–activity relationships of PPAPs.

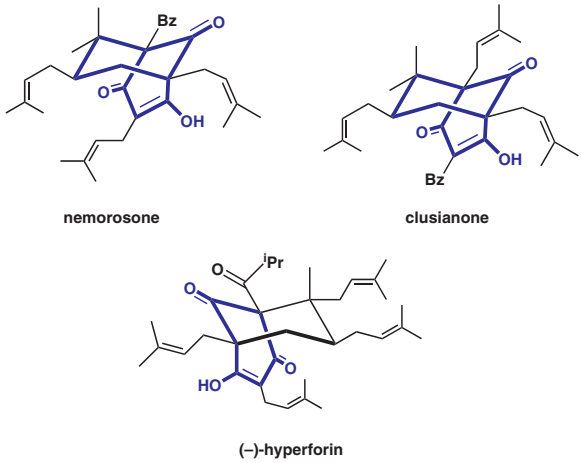
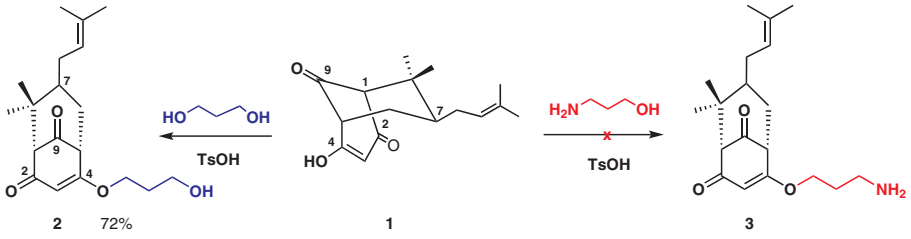


Figure 1 Representative PPAP nature products

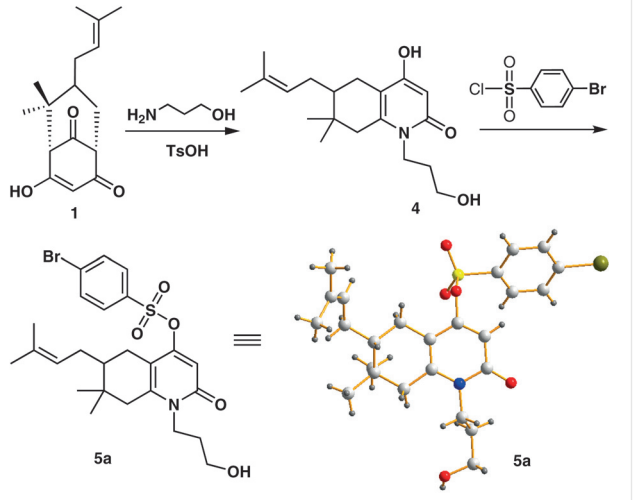
The tetrahydroquinolin-2(1*H*)-one ring system is also important, as it forms the central structural element of numerous natural products that display a wide range of biological activities,[3] such as camptothecins, drug candidates active against leukemia,[4] and others.[5] To date, most protocols for the construction and/or annulation of the tetrahydroquinolin-2(1*H*)-one ring generally involve the conversion of 2-pyrones with ammonia,[6] the oxidation of pyridines,[7] or the Guareschi–Thorpe condensation of acyclic precursors such as cyanoacetamide with 1,3-diketones.[8]



Scheme 1 Modification of the hydroxy group of bicyclic compound **1**

By following the method reported by Spessard and Stoltz,[9] we synthesized bicyclic compound **1** (Scheme 1). We employed several alcohols in an attempt to etherify the hydroxy group on the bicyclic skeleton. In the presence of TsOH, the expected ether **2** was formed when propane-1,3-diol was used (Scheme 1). However, to our surprise, 3-aminopropan-1-ol gave an unexpected product that displayed quite different NMR spectra to ether **2**, whereas the expected product **3** was not detected.

To elucidate the structure of this unknown compound, we attempted to prepared a single crystal, but with no success. We therefore derivatized the compound and found that, fortunately, the corresponding (4-bromobenzene)sulfonyl derivative could be crystallized. A subsequent X-ray analysis indicated that the derivative had structure **5a**, with a highly substituted tetrahydroquinolin-2(1*H*)-one skeleton (Scheme 2). This showed that a unique skeletal rearrangement of the bicyclo[3.3.1]nonane core in **1** had occurred in the presence of the amino alcohol and TsOH. A skeletal rearrangement of a bicyclo[3.3.1]nonane framework had been reported by Couladouros and co-workers,[10] but our result was totally different from theirs. During our work on PPAPs analogues, we explored an impressive skeletal rearrangement of a bicyclo[3.3.1]nonane core that provided a simple alternative route to the synthesis of highly functionalized tetrahydroquinolin-2(1*H*)-ones.

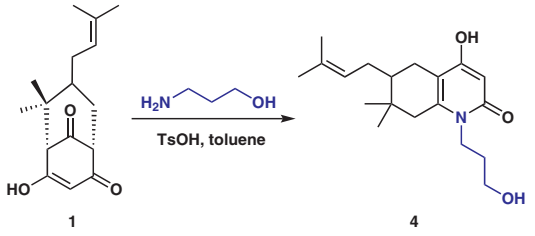


Scheme 2 Preparation of derivative **5a** and its crystal structure

To make this unexpected discovery synthetically useful, we optimized the conditions for the reaction of **1** with 3-aminopropan-1-ol.[11] Initially, we varied the catalyst, the solvent, and the temperature from the original conditions (Table 1, entry 1). A control experiment confirmed that the reaction did not proceed in the absence of the TsOH catalyst (entry 2). Other acids, such as acetic acid, sulfuric acid, or the Lewis acid $CuCl_2$ were tested (entries 3–5). Acetic acid gave a slightly better yield than TsOH (entry 3), whereas the other acids gave complex mixtures. The bases TMEDA and TEA also gave complex mixtures (entries 6 and 7), suggesting that an appropriate acid was necessary for the rearrangement. Among the reaction solvents screened, DMSO and DMF (entries 9 and 10) did not give the desired product. Benzene was a superior solvent to toluene, affording better yield of the desired product (entry 8), but owing to the toxicity and environmentally unfriendly nature of benzene, we continued to use toluene for further screening. The temperature was also crucial in this reaction, as the yield improved greatly at the reflux (entries 11–13). The reaction was almost completed within four hours with a yield of 90% (entry 16). A short reaction time gave insufficient reaction, whereas extending the reaction time resulted in an increase in byproduct formation and lower yields of the required product (entries 13–15). The optimum reaction conditions therefore include the use of 20 mol% of TsOH relative to **1** and two equivalents of 3-aminopropan-1-ol with toluene as the solvent at 120 °C for four hours.

With the optimized conditions in hand, we investigated the substrate scope of the reaction (Scheme 3). When 2-aminoethanol was used, product **4a** was isolated in 78% yield. For amino alcohols with longer alkyl chains (n = 4 or 5), the corresponding products **4b** and **4c** were obtained in moderate yields. Ethane-1,2-diamine and *N*-methylethane-1,2-diamine similarly gave the corresponding products **4d** and **4e**. However, when propylamine was used, the desired product **4f** was not be detected; instead the product in which the C-4 carbonyl group was replaced by an imine was obtained exclusively. This showed that the additional OH or NH group attached to the aliphatic amine plays a crucial

Table 1 Optimization of the Reaction Conditions[a]



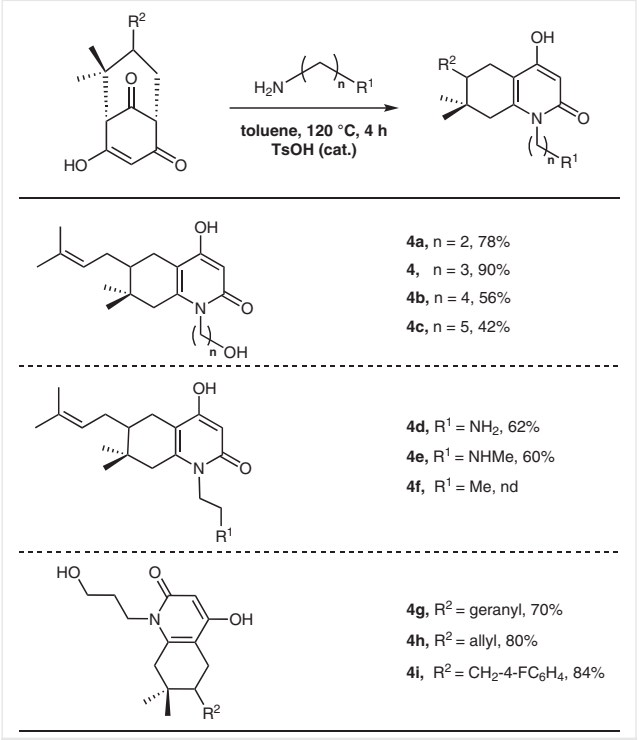
1 4

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	TsOH	toluene	80	8	44
2	–	toluene	80	8	nd[c]
3	HOAc	toluene	80	8	45
4	H_2SO_4	toluene	80	8	–[d]
5	$CuCl_2$	toluene	80	8	–[d]
6	TMEDA[e]	toluene	80	8	–[d]
7	TEA[e]	toluene	80	8	–[d]
8	TsOH	benzene	80	8	61
9	TsOH	DMF	80	8	nd[c]
10	TsOH	DMSO	80	8	–[d]
11	TsOH	toluene	90	8	52
12	TsOH	toluene	100	8	68
13	TsOH	toluene	reflux	8	80
14	TsOH	toluene	reflux	1	86
15	TsOH	toluene	reflux	2	89
16	TsOH	toluene	reflux	4	90

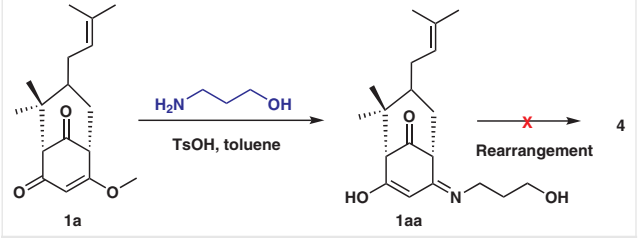
[a] Reaction conditions: **1** (0.5 mmol), 3-aminopropan-1-ol (1 mmol), TsOH (20 mol%).
[b] Isolated yield.
[c] Not detected.
[d] Complex mixture of products.
[e] Two equivalents of the base were used.

role in the rearrangement of the bicyclo[3.3.1]nonane skeleton. To promote the rearrangement, a molecule must possess at least one OH or NH group and one NH_2 group; both functional groups are necessary to drive the rearrangement. Moreover, geranyl, allyl, and 4-fluorobenzyl side chains on the bicyclo[3.3.1]nonane were well tolerated, and the corresponding products **4g–i** were obtained in good yields.

We also found that the C-4 hydroxy-group-protected compound **1a**, gave product **1aa** under the optimized reaction conditions (Scheme 4), and that this could not be converted into **4**, even with a prolonged reaction time. This result suggests that the rearrangement does not start with substitution of the C-4 hydroxy group of **1,** because **1aa** does not transform into the rearrangement product. Thus, **1aa** cannot be an intermediate in the reaction. In addition, the C-4 hydroxy group of **1** must play some other important role in the rearrangement.



Scheme 3 Substrate scope of the rearrangement reaction.



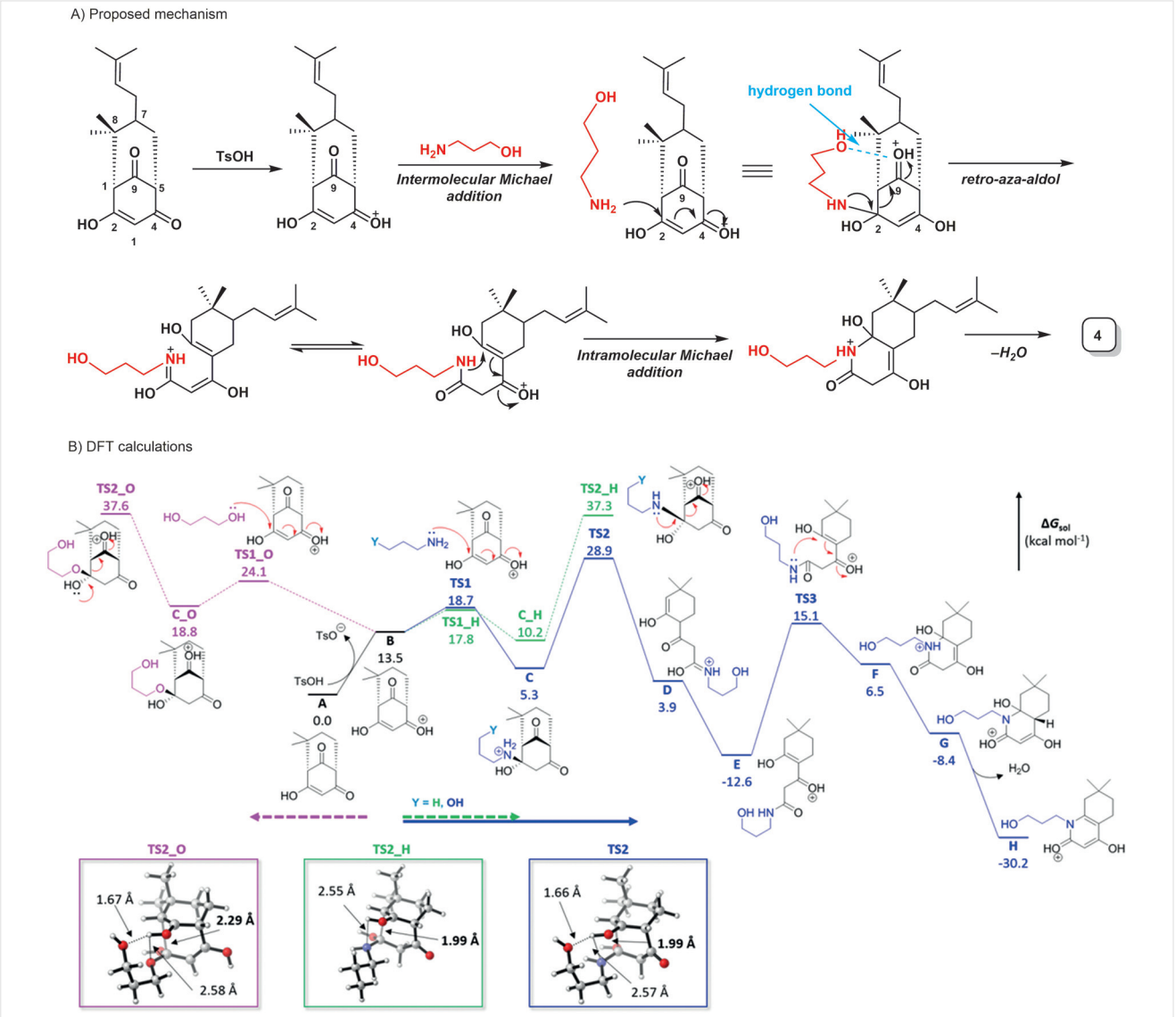
Scheme 4 Control experiment.

On the basis of the above findings, a possible mechanism including several transformations is proposed (Scheme 5). Although we made considerable efforts to capture the rearrangement intermediates, we unfortunately failed to do so. Consequently, we conducted a detailed computational study by density functional theory (DFT; M06-2X with solvation) calculations to explore the mechanism of the unique reaction.[12] The computed free energies for the skeletal rearrangement of bicyclic compound **A** (in which the 3-methylbut-2-enyl side chain of the bicyclic compound **1** was replaced by a hydrogen atom to simplify the calculation) with 3-aminopropan-1-ol in the presence of TsOH are summarized in Scheme 5(B) (blue). To reveal why the rearrangement does not occur when a diol or simple amine is employed, the free energies for the reactions of bi-

cyclic compound **A** with propane-1,3-diol (pink) or propylamine (green) were also computed and are shown in Scheme 5(B).

For the skeletal rearrangement reaction of bicyclic compound **A** with 3-aminopropan-1-ol [blue lines, Scheme 5(B)], the DFT calculations indicate that the overall process involves an intermolecular Michael addition (via **TS1**), a retro-aza-aldol reaction (via **TS2**),[13] and an intramolecular Michael addition (via **TS3**), followed by dehydration to give the final product. Various isomers were considered for each intermediate and transition-state structure, and the lowest-energy ones are presented in Scheme 5(B). The rate-determining step is the retro-aza-aldol reaction, which has an overall energy barrier of 28.9 kcal/mol in toluene.

The reaction with propane-1,3-diol [Scheme 5(B); pink lines] has a high activation-energy barrier of 37.6 kcal/mol (via **TS2_O**), and therefore the rearrangement is not likely to occur under the current reaction conditions (an etherification occurred experimentally; see Scheme 1). Compared with the reaction with 3-aminopropan-1-ol, the difference in the overall energy barrier (37.6 versus 28.9 kcal/mol) arises mainly from the difference in the thermodynamic stability of the intermolecular Michael addition products **C_O** and **C** (18.8 versus 5.3 kcal/mol), although the retro-aldol step from intermediate **C_O** has a barrier of only 18.8 kcal/mol. The superior nucleophilicity of an amine compared with an alcohol makes the intermolecular Michael addition step more favorable both kinetically and



Scheme 5 (A) Proposed mechanism. (B) DFT-computed free energies for the reactions of bicyclic compound **A** with 3-aminopropan-1-ol (blue lines), propane-1,3-diol (pink lines), and propylamine (green lines) in the presence of TsOH. Key transition structures are shown at the bottom.

thermodynamically, leading to a lower overall barrier for the skeletal rearrangement reaction. This explains why the diol is not suitable for this reaction.

The computed rearrangement barrier for the reaction using propylamine [Scheme 5(B); green lines] is also very high (37.3 kcal/mol via **TS2_H**), in agreement with the experimental result that the skeletal rearrangement product was not detected (**4f**; Scheme 3). When comparing the structures of two retro-aza-aldol transition states **TS2** and **TS2_H**, it is clear that hydrogen bonding between the OH group attached to the aliphatic amine and the protonated ketone in **TS2** (1.66 Å, Scheme 5B) stabilizes the retro-aza-aldol transition state significantly (28.9 versus 37.3 kcal/mol). This indicates that the hydroxy group of the amino alcohol plays a key role in the retro-aza-aldol reaction step and, consequently, the simple amine does not work in the reaction.

In conclusion, the bicyclo[3.3.1]nonanetrione skeleton of PPAPs can be transformed into a 4-hydroxytetrahydroquinolin-2(1*H*)-one through a unique rearrangement reaction. The reaction mechanism was rationalized by DFT calculations. The method provides a simple route for the synthesis of derivatives of 4-hydroxytetrahydroquinolin-2(1*H*)-one.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610187.

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(11) **4-Hydroxy-1-(3-hydroxypropyl)-7,7-dimethyl-6-(3-methylbut-2-en-1-yl)-5,6,7,8-tetrahydroquinolin-2(1*H*)-one (4)**
A 250 mL round-bottomed flask was charged with bicyclic compound **1** (1.3 g, 5.0 mmol, 1.0 equiv) in toluene (100 mL). TsOH·H_2O (20 mol%) was added, followed by 3-aminopropan-1-ol (0.8 mL, 10.0 mmol, 2.0 equiv). The flask was fitted with a

Dean–Stark head and a condenser, and the mixture was heated at 120 °C for 4 h. The mixture was then concentrated to a brown oil that was purified by chromatography (silica gel, 1–3% MeOH–CH_2Cl_2) to give a white foam; yield: 1.4 g (90%); R_f = 0.40 (10% MeOH–CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (s, 1 H), 5.15 (t, *J* = 7.0 Hz, 1 H), 4.32–4.19 (m, 1 H), 4.16–4.02 (m, 1 H), 3.54 (s, 2 H), 2.68 (dd, *J* = 17.7, 5.5 Hz, 1 H), 2.44 (s, 2 H), 2.32–2.20 (m, 1 H), 2.08 (dd, *J* = 17.6, 9.6 Hz, 1 H), 1.88–1.79 (m, 2 H), 1.79–1.71 (m, 1 H), 1.70 (s, 3 H), 1.59 (d, *J* = 1.2 Hz, 3 H), 1.40 (m, 1 H), 1.07 (s, 3 H), 0.87 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.63, 165.31, 142.97, 132.54, 123.08, 110.76, 96.93, 58.16, 41.85, 41.45, 39.45, 32.77, 32.23, 28.85, 27.90, 25.86, 24.77, 21.35, 17.81. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{30}NO_3$: 320.2225; found: 320.2211.

(12) Geometries of minima and transition structures were optimized at the level of M06–2X with the 6–31G (d) basis set. Solvent effects in toluene were evaluated on the gas-phase optimized structures by using the CPCM model at the M06–2X/6–311+G(d,p) level. For details, see the Supporting Information.

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