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Scaffold Diversity

Diversity-Oriented Synthesis of Polycyclic Scaffolds by Modification of an Anodic Product Derived from 2,4-Dimethylphenol**

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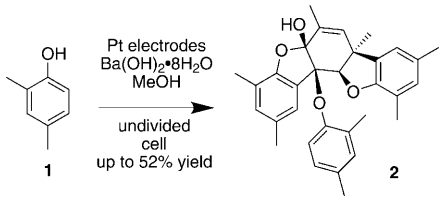
One of the biggest challenges facing the biologists and chemists is understanding the mechanisms that control biological processes.[1] The structures of the chemical compounds involved in these mechanisms determine their role, for example, as drugs or as proteins with given functions. To understand the role a particular compound plays in a biological process, its chemical profile must be determined. Screening experiments carried out with compound libraries are used to search for the discrete target displaying the desired properties. In this search, libraries of compounds showing a broader diversity of frameworks span larger tracts of biologically relevant chemical space,[2] making it easier to identify lead molecules.[3] Organic chemists use a limited range of functional groups for synthesizing compounds based on already known architectures;[4] hence generating structural complexity and diversity is crucial in the creation of compound collections for biological screening.[5] The synthesis of target molecules and medicinal chemistry in general cover a limited chemical space, since at most only a diversity of functional groups is possible. For this reason a concept with more structural flexibility is needed. Diversity-oriented synthesis (DOS) focuses on the generation of structurally diverse scaffolds in the fewest possible steps.[6] This new field of organic chemistry covers a broader chemical space by using diversity-generating reactions to achieve high substitutional, stereochemical, and skeletal diversity. DOS can be achieved by biomimetic transformations[7] and functional-group pairing,[8] as well as by convergent,[9] domino,[10] and cascade[11] approaches and multicomponent reactions.[12] In these approaches the particular emphasis is on innovations that allow skeleton modification.[13] Recently, Moeller and coworkers developed a electrochemical protocol for the synthesis of addressable libraries as platforms for biological assays on microelectrode arrays.[14] Electrochemical reactions have been used as the key step in the synthesis of complex molecules.[15] Herein, we report a new electrochemically based DOS protocol, in which the electrooxidation of 2,4-dimethylphenol is the key reaction for the complexity-generating strategy.

The electrooxidation of 2,4-dimethylphenol (**1**) on Pt electrodes using $Ba(OH)_2 \cdot 8H_2O$ in methanol as electrolyte affords compound **2** (Scheme 1).[16] This dehydrotetramer of



Scheme 1. Electrooxidation leading to the key intermediate **2**.

2,4-dimethylphenol can be obtained in large quantities (up to 23 g per run) and is easily isolated since it precipitates during electrolysis in an undivided cell. The formation of **2** takes place with exclusive diastereoselectivity; most probably the divalent cation Ba^{2+} brings together the initially formed Pummerer ketone derivative and another unit of **1** in a defined orientation.[17] Scaffold **2** shows a range of functionalities for subsequent diversity-generating reactions (Scheme 2). Similar to a Swiss Army knife, wherein a simple action provides a distinct function or tool, simple transformations applied to the richly functionalized intermediate **2** led to 14 compounds with 11 different scaffolds in good to excellent yield. The optimized reactions provide a library of novel polycyclic architectures. By manipulating the reaction conditions we could create molecules with alternative scaffolds, the cornerstone of diversity-oriented synthesis, and achieve stereo-, regio-, and chemoselectivity control.

When the anodically produced key intermediate **2** is treated either thermally,[16] or more efficiently with acid, the spiropentacycle **3** is obtained exclusively.[17] In the cationic intermediate a stabilizing secondary orbital interaction might exist between the lone pairs of electrons on the oxygen atoms and the empty orbital (Scheme 3). This interaction suggests a late transition state. Most remarkably, blocking the hydroxy group of the hemiketal moiety of **2** with acid-labile groups greatly influences the course of the reaction. The silylation reaction can be performed under standard conditions, providing, for example, the *O*-TIPS-protected **4c** in good yield (86%). It is noteworthy that the hemiketal is not opened up. Treatment of these silylated substrates with Lewis acids results in the preferential formation of **5**, an epimer of **3** in which the spiro center is inverted (Scheme 2). The acid lability of the silyl groups is directly reflected in the **3**/**5** ratio

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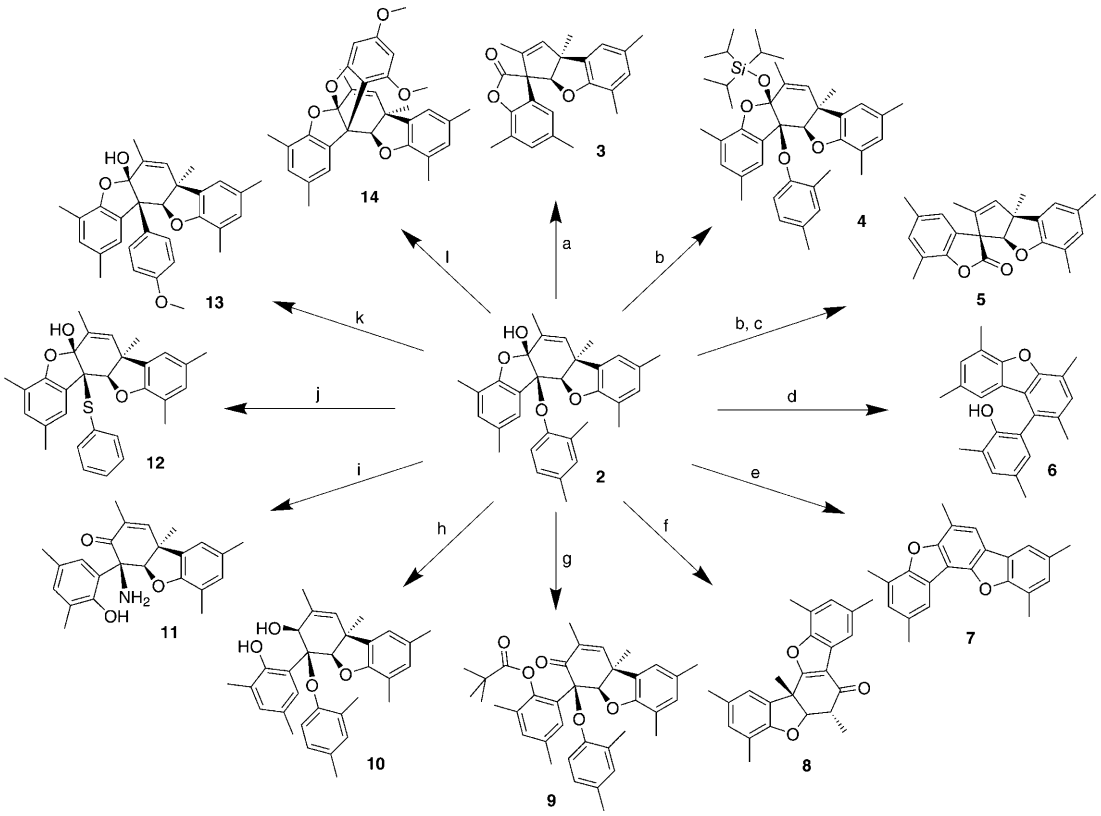


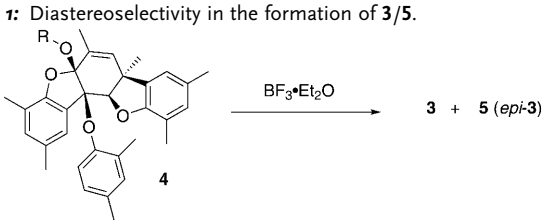
Scheme 2. Diversity-oriented strategy. Reagents and conditions: a) conc. H_2SO_4, toluene, RT, 4 h, 75%; b) 2,4-lutidine (4 equiv), TIPSOTf (3 equiv), CH_2Cl_2, RT, 7 days, 86%; c) $BF_3{\cdot}Et_2O$ (3.5 equiv), CH_2Cl_2, RT, 12 h, 62%; d) Et_3SiH (2 equiv), TFA (2 equiv), CH_2Cl_2, RT, 24 h, 80%; e) $SOCl_2$ (1.5 equiv) CH_2Cl_2, RT, 7 days, 59%; f) NaCN (4 equiv), CH_3CN, 80°C, 24 h, 82%; g) PvCl (4 equiv), DMAP (1%), NEt_3 (4 equiv), CH_2Cl_2, RT, 2 days, 81%; h) $LiAlH_4$ (1 equiv), THF, 0°C to RT, 24 h, 76%; i) NH_4F (4 equiv), CH_3CN, 80°C, 24 h, 67%; j) thiophenol (2 equiv), $BF_3{\cdot}Et_2O$ (2 equiv), CH_2Cl_2, −78°C to RT, 99%; k) anisole (2 equiv), $BF_3{\cdot}Et_2O$ (1 equiv), CH_2Cl_2, −78°C to RT, 50%; l) 3,5-dimethoxyphenol (1.1 equiv), $BF_3{\cdot}Et_2O$ (4 equiv), CH_2Cl_2, −78°C to RT, 94%. TIPSOTf = triisopropylsilyl triflate, TFA = trifluoroacetic acid, PvCl = pivaloyl chloride, DMAP = 4-dimethylaminopyridine.

(Table 1). The trimethylsilyl-protected substrate **4a** provides a mixture of **3** and **5** in a 30:70 ratio (Table 1, entry 1). When the silyl groups are bulkier, the yield of **5** increases and the transformations are significantly cleaner (Table 1, entries 2 and 3).

A mechanistic rationale is given in Scheme 3. Liberation of 2,4-dimethylphenol from **4** generates the cationic species **I**. Repulsion of the lone pairs of the oxygen functionalities paves the way to **3**. When silyl-protected substrates are used, the rearrangement of cation **II** is disfavored on the *Re* side and consequently, the less sterically demanding pathway leads to **5**. The stereochemical course of the Wagner–Meerwein rearrangement can be efficiently altered by the use of a proton equivalent. The rearrangement of the silylated species occurs in almost 70% total yield (Table 1). The bulk of the silyl moieties directs the skeletal rearrangement since cleavage of the silyl moiety seems to be the final step. Complete stereochemical reversal and exclusive formation of **5** is probably not possible, since the desilylation seems to occur under electrophilic conditions to some extent prior to the rearrangement. When typical conditions for ionic hydrogenation are applied to **2**,[18] dibenzofuran **6** is formed as the sole product by reduction of the benzylic position, elimination of water, ring opening, and 1,2-shift. Thus **6** is obtained from **1** in only two simple preparative steps (a mechanistic rationale is given in the Supporting Information).

Treatment of key intermediate **2** with thionyl chloride leads to the demethylation of a quaternary carbon atom of the central carbocycle. A sequence of elimination reactions results in the pentacyclic heteroaromatic system **7** (a mechanistic rationale is given in the Supporting Information). Treatment of **2** with cyanide as a potent nucleophile alters the connectivity of the polycyclic scaffold and provides **8** in 82% yield. The mechanistic proposal includes ring opening of the

Table 1: Diastereoselectivity in the formation of **3**/**5**.



Entry	R	**3**/**5**	Yield of **5** [%]
1	$Si(CH_3)_3$ (**4a**)	30:70	47
2	$Si(CH_2CH_3)_3$ (**4b**)	25:75	53
3	$Si(CH(CH_3)_2)_3$ (**4c**)	10:90	62

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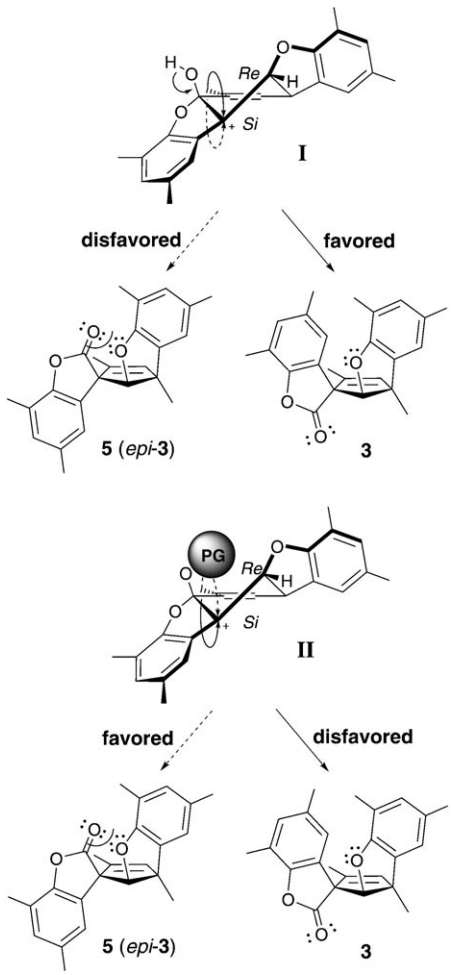

Scheme 3. Diastereoselective formation of **3** and **5.** Pathway for the intermediate starting from **2** (top) and reaction course of silylated species (bottom).

hemiketal, elimination to the α,β-unsaturated system, and subsequent ring closure (see the Supporting Information).

The hemiketal portion of **2** can be modified under mild conditions without affecting the rest of the structure. Esterification with pivaloyl chloride provides cyclohexenone **9** in 81 % yield. Treatment with $LiAlH_4$ gives the highly functionalized cyclohexenol **10** as a single diastereomer. In reactions with good nucleophiles the 2,4-dimethylphenoxy substituent of **2** can be replaced. Subjecting **2** to ammonium fluoride in acetonitrile installs the amino group on a benzylic position and simultaneously cleaves the hemiketal. To our knowledge no similar conversion has been reported. The excellent hydrogen-bond-donating capabilities of the phenolic moiety leads to an intramolecular hydrogen bond to the amino function while liberating the central cyclohexenone **11**. Replacement of the oxygen-bound aryl moiety in **2** by thiols requires low temperatures. Under these conditions **12** is formed quantitatively, whereas at ambient temperatures redox transformations lead to diaryl disulfides and benzofuran **6**. At low temperatures Friedel–Crafts chemistry is accessible while the pentacyclic architecture is conserved. When anisole is used as a carbon nucleophile, the arylation reaction occurs exclusively at the 4-position of anisole and product **13** is obtained. This particular scaffold is remarkably similar to the naturally occurring rocaglamide (see the Supporting Information), a secondary metabolite from

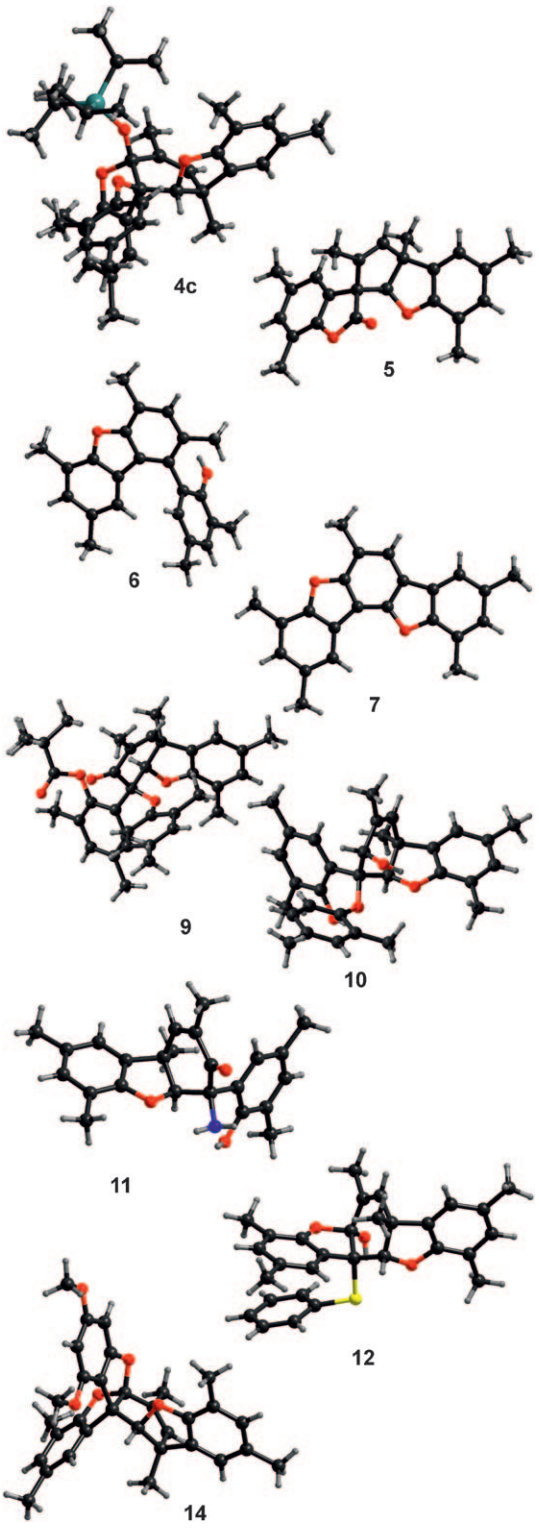

Figure 1. X-ray crystal structures of the novel polycycles. Dark gray C, light gray H, blue N, red O, yellow S, turquoise Si.

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Aglaia elliptifolia, isolated in 1982 by King et al.[19] Rocaglamide and its more than 50 isolated derivatives exhibit insecticidal and cytotoxic activity against several cancer cell lines.[20] Its characteristic cyclopenta[*b*]benzofuran core has five contiguous stereocenters in the cyclopentane ring. The unusual structure of rocaglamide, combined with its interesting biological activity, has attracted the interest of industrial and academic researchers.[21] If the arylation reaction leading to **13** is conducted with a reaction partner equipped with an additional hydroxy group *ortho* to the newly formed C–C bond, the propellane derivative **14** is produced in excellent yield.

The structural assignment of the obtained products was challenging since the polycyclic products show suitable but not unequivocal NMR data. For almost all new scaffolds, X-ray analyses of suitable single crystals could be performed. Consequently, the structural elucidation was feasible. Molecular structures of these novel scaffolds based on X-ray data are depicted in Figure 1. Further details on the individual architectures and crystal packing are provided in the Supporting Information.

In conclusion, we have found a simple way to create molecular complexity by anodic oxidation of 2,4-dimethylphenol. The resuling dehydrotetramer **2** can be transformed into an variety of scaffolds depending on the applied reaction conditions. In our approach, the polycyclic architectures can be prepared in two or three steps from 2,4-dimethylphenol with almost exclusive selectivity and in reasonable yields. Skeleton rearrangements are induced at higher temperatures, whereas lower temperatures allow manipulations at the periphery. Several of the molecular architectures obtained are similar to known natural products (see the Supporting Information). Polycyclic phenol oxidation products with similar complexity may also occur during the "oxidative burst", a defense mechanism of plants against fungal infection.[22] In this oxidation coniferyl alcohol is randomly coupled by reaction with reactive oxygen species.[23] Consequently, our polycyclic compounds might have antifungal potential. The biological profile of these structures will be reported in due course.

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