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Installation of Amine Moieties into a Polycyclic Anodic Product Derived from 2,4-Dimethylphenol

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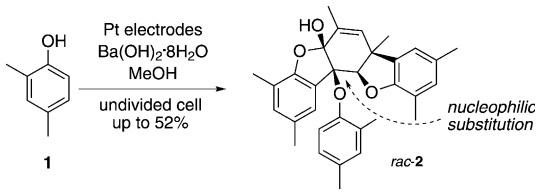
Abstract: When 2,4-dimethylphenol is anodically treated, a dehydrotetramer with four contiguous stereocentres is readily obtained on a multi-gram scale. The substitution of a 2,4-dimethylphenoxy fragment by several amines was demonstrated, and the best results were obtained with primary amines. Optically pure α-chiral aliphatic amines yield diastereomeric mixtures that can be separated in most cases. The basic amine causes a partial hemiketal-opening of the bisbenzofuran moiety leading to an equilibrium within an α,β-unsaturated cyclohexenone. This dynamic behaviour occurs on the time scale of NMR spectroscopy and is also found by X-ray analysis providing a consistent picture.

Keywords: amination · chiral resolution · diastereoselectivity · hemiketal formation · polycycles

Introduction

Enantiomerically pure compounds are especially valuable in modern organic synthesis. Resolution of racemic mixtures and stereoselective reactions of chiral or prochiral starting materials are the two major routes to obtain optical enrichment.[1]

Even though asymmetric approaches offer distinct advantages, diastereomer-mediated resolution is still the method of choice for large-scale enantiomer separations,[2c] mainly due to the robustness of the processes and the availability of various natural and synthetic agents.[1,2] Synthetic challenges thereby often consist in the generation of multiple well-defined stereogenic centers, for example, by using domino approaches[3] or multicomponent sequences.[4] The electron-rich 2,4-dimethylphenol **1** was shown to be a potent starting material in electro-organic synthesis[5] and can be converted easily and efficiently to polycyclic dehydrotetramer *rac*-**2** (Scheme 1).[6] This step appears to be a complexity-generating reaction and confirms electrochemically induced oxidative couplings of phenols as a powerful methodology in diversity-oriented synthesis.[7] In subsequent studies, compound **2** was identified as a promising platform for the synthesis of structurally diverse polycycles, providing a diversity-oriented compound library.[7] Starting from **1**, eleven different scaffolds can be obtained through highly chemo-, regio- and stereoselective reaction sequences in only two synthetic steps. We assume that the unique combination of hydrogen-bonding interactions and 1,3-diaxial repulsions for the attack from the lower side is responsible for the high degree of diastereoselectivity in these substitution reactions (Figure 1).[8]



Scheme 1. Dehydrotetramer *rac*-**2** obtained by anodic treatment of **1** and its reactivity.

Dehydrotetramer **2** represents the key intermediate that provides a densely functionalized cyclohexene core

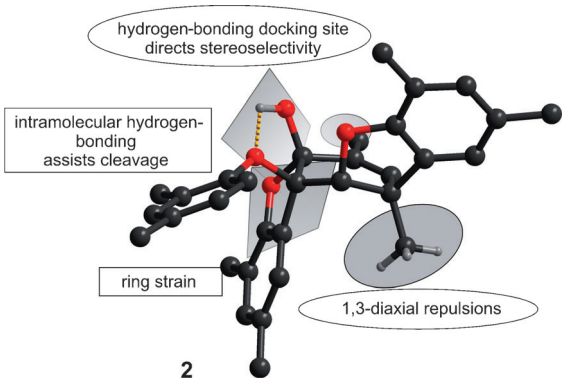


Figure 1. Key interactions for the stereoselective substitution of the phenoxy moiety in dehydrotetramer **2**.

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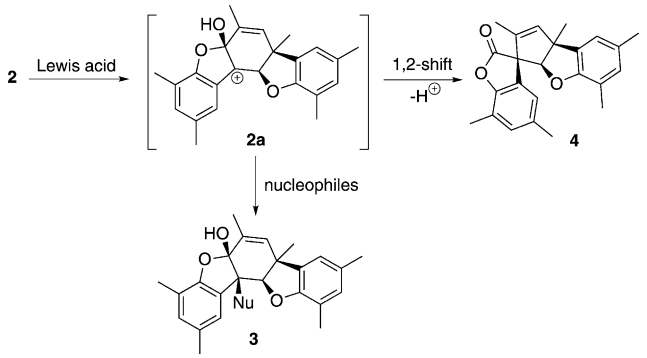


Scheme 2. Formation of carbocation **2a** and its reaction pathways, leading to nucleophilic substitution (**3**) and semipinacol-type rearrangement product **4**.

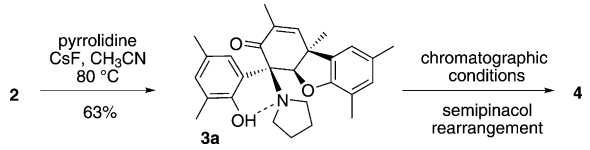
equipped with four contiguous stereocentres. Treatment with Lewis or Brønsted acids cleaves the 2,4-dimethylphenoxy moiety, generating the tertiary carbocation **2a**. This intermediate opens up the possibility to introduce molecular variation into the scaffold by simply switching the reaction conditions (Scheme 2). In general, the central scaffold can be conserved at low temperatures and the generated carbocation **2a** can be used for the selective conversion with nucleophiles.[7,8] Raising the temperature changes the reactivity, and skeletal rearrangement (as typically expected for carbocations) becomes dominant. This pathway yields complex architectures such as spirocycle **4** in a highly selective manner.[7]

The molecular structure of **2** seems to be a promising platform for the synthesis of natural product analogues.[7] Hence, its modification might open an easy access to novel pharmacologically active structures. For instance, spiropentacycle **4** contains a central cyclopenta[*b*]benzofuran moiety, which has been regarded as the biologically active component in natural products of the rocaglamide family.[9] In previous studies, the stereospecific substitution of one phenoxy fragment by an amino group was achieved. This amination reaction was found upon treatment of **2** with NH_4F in acetonitrile at 80 °C.[7] An intramolecular hydrogen-bonding between the hydroxy group of the hemiketal (donor) and the phenol ether moiety (acceptor) of **2** might decrease the LUMO energy level of the latter,[10a] activating it towards nucleophilic substitution (Figure 1). Their arrangement at the same side of the central cyclohexene ring forms an ideal docking site for incoming nucleophiles. On the other hand, one methyl group at the cyclohexene points to the other side of the molecule and leads to 1,3-diaxial repulsions. Both effects are responsible for the high diastereoselectivity in nucleophilic substitution reactions (Figure 1).[7,8] When no good nucleophiles enter the reaction scene, several rearrangements of the backbone have been observed resulting in complex molecular architectures.[7] Herein, we present the nucleophilic substitution of the 2,4-dimethylphenoxy moiety using optically pure α-chiral aliphatic or benzylic amines and subsequent resolution of the diastereomeric species.

Results and Discussion

Upon oxidative treatment, phenols can undergo the formation of polycycles instead of the anticipated *ortho–ortho* coupling reaction. The most common structural motif is the so called Pummerer's ketone, which is obtained as a result of an *ortho–para* coupling and a subsequent 1,4-addition.[11] In particular, 2,4-dimethylphenol is prone to the formation of this architecture. When anodic protocols are applied, the generation of larger dehydro-oligomers is observed.[6a] Derivative **2** seems to be the key intermediate for most of the pentacyclic architectures found. When using an undivided cell equipped with platinum electrodes and $Ba(OH)_2{\cdot}8H_2O$ in methanol as electrolyte, **2** can be readily obtained by electrolysis under constant current control. Compound **2** precipitates during the electrolysis and can be isolated in almost pure fashion by simple filtration (Scheme 1).[6b] This simple protocol yields up to 24 g of **2** per run (52 % yield), providing significant amounts for subsequent reactivity studies. The complex central ring of **2** is formed in exclusive stereoselectivity. The proposed mechanism suggests the Pummerer's ketone derivative as an intermediate in the formation of **2**.[6] Since the derivative of Pummerer's ketone is obtained as a mixture of enantiomers, dehydrotetramer **2** is provided as a racemate. Diastereomer-mediated resolution with enantiomerically enriched auxiliaries seemed to be the best way to separate the generated diastereomers. In initial studies, the hydroxyl group of the hemiketal was successfully modified by silylation or opened up by *O*-acylation of the phenolic portion.[7] Several resolving agents including (−)-camphanic acid chloride were found to be unsuitable for resolving racemic **2**.

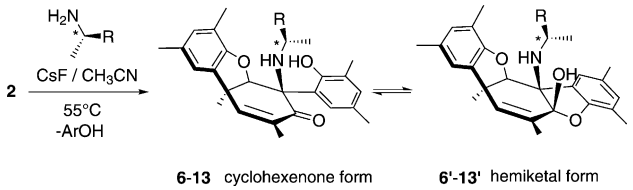
Therefore, the displacement of the 2,4-dimethylphenoxy moiety by a removable auxiliary should be a viable route. We decided to expand the amination reaction of **2** and to introduce aliphatic amines with stereogenic information. To the best of our knowledge, no similar transformation has been previously reported. To explore the scope of this reaction, compound **2** was initially treated with pyrrolidine and CsF as fluoride source in acetonitrile heated to reflux, whereby the expected tertiary amine **3a** was obtained in 63 % yield (Scheme 3). X-ray diffraction experiments of suitable single crystals confirmed the anticipated structure. Remarkably, in the solid state **3a** is obtained in the ring-opened cyclohexenone form. One reason for this observation is the formation of hydrogen bonding between the basic pyrrolidine nitrogen (protonated moiety: pK_a 10.46[12a]) and the neighbouring hydroxyl hydrogen of the weak acid



Scheme 3. Formation of amino derivative **3a** and its rearrangement to spiropentacycle **4**.

phenol (pK_a 10.59[12b]). Therefore, **3a** exhibits intramolecular hydrogen bonding from the phenol donor to the pyrrolidine acceptor with a bond distance d(O···N) = 2.685(2) Å. Tertiary amine **3a** turned out to be unstable under prolonged preparative and harsh analytical conditions. Thermal impact upon gas chromatography or column chromatography on silica cleaves off the pyrrolidine ring. The generated carbocation undergoes a semipinacol rearrangement to finally yield spirolactone **4**. This pathway provides an access to the initially targeted structure **4**.

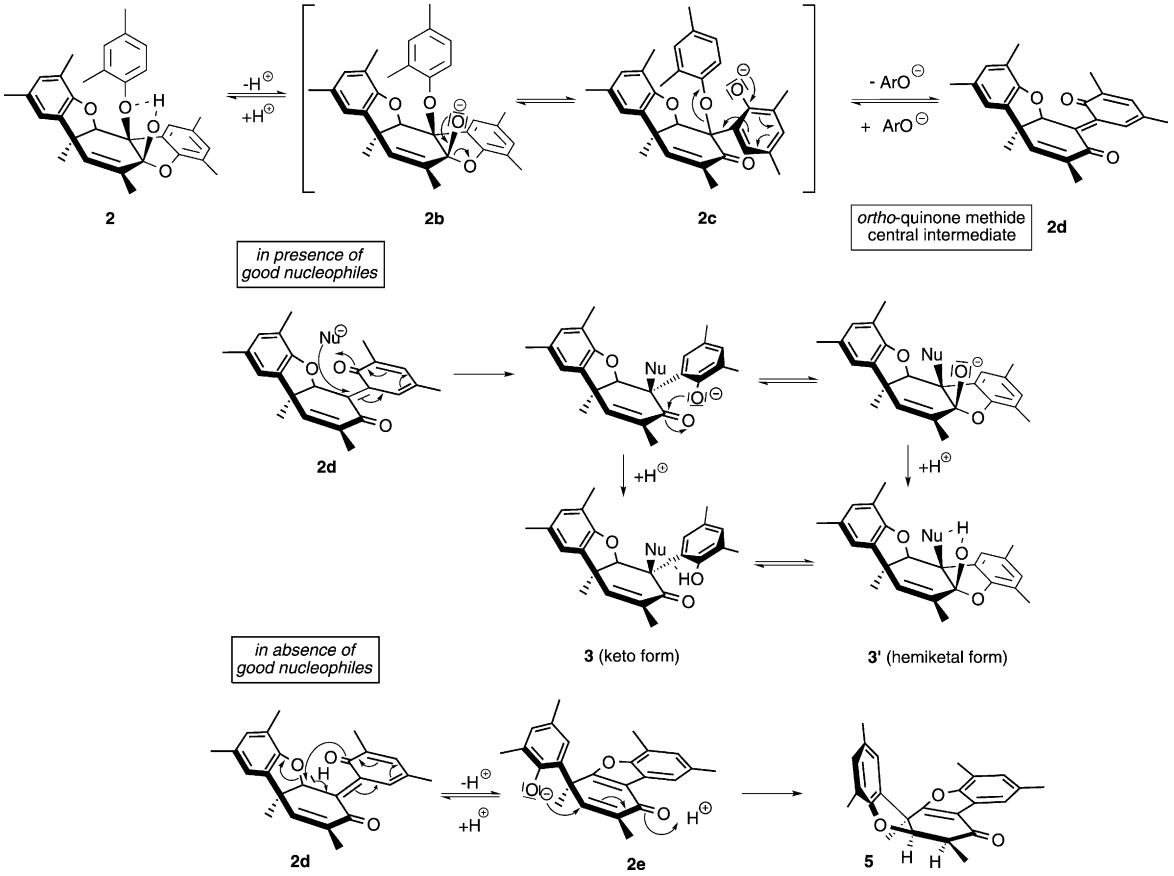
Initial experiments using L-proline ethyl ester or amino alcohol (−)-ephedrine did not lead to the desired products, instead, compound **5** was predominantly obtained. Pentacycle **5** was first isolated as a minor component during the electrochemical oxidation of **1**[6a] and can also be obtained in high yields after treating **2** with NaCN.[7] Since α-substituted secondary amines exhibit an enhanced steric demand, they are non-suitable substrates for this substitution reaction on the densely functionalized polycycle **2**. Therefore, we focused our investigations on optically pure primary amines, furnishing optically pure polycycles **6**–**13** (Scheme 4). Substoichiometric amounts of CsF (30 mol%) and lower temperatures (55 °C) were found to be milder reaction conditions. Further studies using other alkali fluorides also led to a nucleophilic replacement of the phenolether moiety by the amine, but



Scheme 4. Reaction of **2** with optically pure amines under formation of substitution products, equilibrating between cyclohexenone (**6**–**13**) and hemiketal form (**6′**–**13′**).

neither the yield nor the reaction rate could be increased. We initially anticipated an activation of the nucleophile through hydrogen bonding by fluoride, as previously reported in fluoride-catalysed N-alkylation reactions.[12] When using Cs_2CO_3, the amination reaction occurred as well, revealing that the fluoride acts mostly as a base.

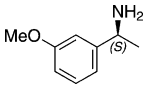
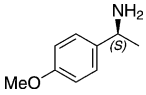
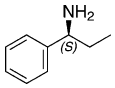
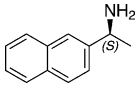
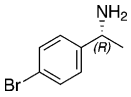
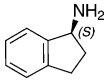
From mechanistic rationale these results indicated that derivatives **3** and **5** originate from a common intermediate derived from **2**, which might be explained by the following assumption (Scheme 5): Under basic conditions, the hemiketal moiety **2** will be deprotonated and opened up to give the stabilized α,β-unsaturated system **2c**. Extrusion of the 2,4-dimethylphenolate yields the *ortho*-quinone methide **2d**. *ortho*-Quinone methides have been suggested as synthetic



Scheme 5. Mechanistic rationale for the amination reaction to yield nucleophilic substitution products as exemplified on derivative **3**, and an alternative pathway for the formation of **5**.

intermediates in multiple mechanistic pathways.[14] In nature, this facile activation of the benzylic position by tautomerization takes place without enzymatic intervention. Compound **2d** represents a key intermediate in our mechanistic rationale and determines the reaction pathway. Additionally, compound **2d** is a highly conjugated π-system containing two dipoles that compensate each other and a lower steric demand compared with the starting material. If nucleophilic amines (Table 1) are present, a 1,4-addition followed by protonation

Table 1. Scope of the substitution reaction with optically pure amines.

Entry	Amine	Diastereoisomers	Yield [%][a]	Ratio of ketone to hemiketal
1		**6a**	38	0:1[b]
		6b	41	1:1[b]
2		**7a**	37	–[c]
		7b	44	–[c]
3		**8a**	42	1:0.38[d]
		8b	42	1:0.47[d]
4		**9a**	39	1:0.36[b]
		9b	42	1:0.63[b]
5		**10a**	40	0.22:1[d]
		10b	42	0:1[d]
6		**11a**	30	1:0.31[d]
		11b	37	1:0.5[d]
7		**12a/b**	75	1:0.4[e]
8		**13a/b**	77	1:0.13[d]

[a] Refers to isolated product yields. [b] Ratio determined at −20 °C. [c] Ratio could not be determined due to strong signal broadening. [d] Ratio determined at 20 °C. [e] Ratio determined at 25 °C.

provides amino derivatives **3** and **6–13** with exclusive stereoselectivity. In the absence of suitable nucleophiles, the loss of the proton in the vinylogous position induces a domino-type ring-opening/ring-closure sequence (**2d**→**2e**) to finally furnish pentacycle **5**.

To elucidate the scope of this transformation and explore the possibilities for the separation of the diastereomeric products, we introduced different primary aliphatic as well as benzylic amines as nucleophiles.

By using a twofold excess of the amine component and applying the mild reaction conditions, we were able to replace the phenoxy moiety. Filtration over silica as stationary phase and cyclohexane/ethyl acetate (9:1) as eluent allowed us to remove polar side products such as 2,4-dimethylphenol (**1**) and the excess of amine. Subsequent column chromatography on silica with a less polar eluent system (e.g., cyclohexane/ethyl acetate 20:1) led to the desired compounds as mixture of diastereoisomers that were assigned by means of NMR spectroscopy, MS, HRMS, EA, RP-HPLC as well as X-ray analysis of suitable single crystals (Figures 2 and 3 and the Supporting Information). The results of these studies are listed in Table 1. The isolated overall yields of isomeric pairs of **6–13** are fairly good and range from 67 to 84 %. We were able to explore the scope of this approach and successfully separate the diastereoisomers **6–11** (in yields ranging from 30–44 %). In case of **12** and **13** it is possible to introduce optically pure amine moieties, but resolution of the generated diastereomers was found to be impossible. Moreover, we were able to separate both diastereoisomers by analytical reversed-phase high-performance liquid chromatography (RP-HPLC), but failed to separate them when applying column chromatography.

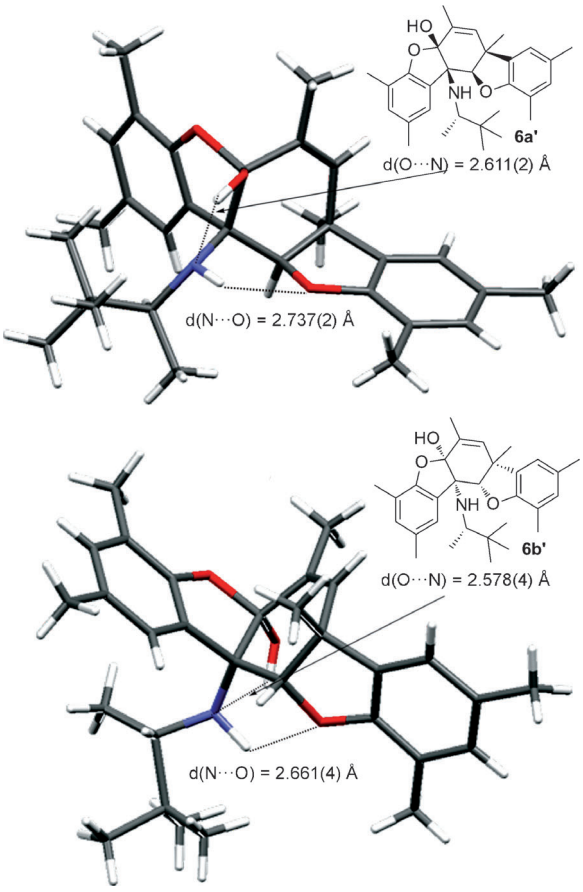


Figure 2. Molecular structures of diastereoisomers **6a′** (top) and of **6b′** (bottom) obtained by X-ray analysis (different crystals).

The structure of two representative pairs of diastereoisomers **6a–b** and **9a–b** were confirmed in chloroform at −20 °C by assigning their NMR chemical shifts by using routine techniques (^{1}H, ^{13}C, HMBC, HSQC, NOESY). In addition, the relative configuration of the diastereomeric pair of **6** was proven by single-crystal analysis of suitable crystals (Figure 2). In contrast to the trends found by NMR experiments (see the Supporting Information) and to the X-ray

structure of **3a**, which exists in the cyclohexenone form, in the solid state these molecules exist in form of their hemiketals **6a′/b′**. Thereby, hydrogen bonding of the amine proton to the adjacent dihydrobenzofurane moiety (**6a′**, d(N···O) = 2.737(2) Å) as well as from the hemiketal hydroxyl group to the amine nitrogen (**6a′**, d(O···N) = 2.611(2) Å) was observed (Figure 2).

As proven by NMR measurements, the amino derivatives coexist in an equilibrium between their carbonyl (**6**–**13**) and hemiketal form (**6′**–**13′**, Scheme 4 and the Supporting Information). Both, the cyclohexenone and the hemiketal form of each diastereoisomer can be clearly distinguished due to their characteristic shifts. The benzylic proton of the amine moiety for instance, shows a characteristic quartet signal in the ^{1}H NMR spectrum between δ = 3.5 and 4.5 ppm. In ^{13}C NMR spectra, the α,β-unsaturated cyclohexenone ring of **3** exhibits a weak broadened signal for the carbonyl group at approximately δ = 205 ppm, whereas the carbon of the hemiketal causes a sharp signal at higher field (ca. δ = 106 ppm). Due to the different ^{1}H NMR signals it is possible to estimate the relative ratio of both equilibrating forms. In addition, the carbonyl derivatives exhibit significantly higher molecular flexibility. This in turn will impede the formation of regularly ordered molecules and might explain the preferred crystallisation of hemiketal derivatives **6′**–**13′** from this equilibrium. Structure elucidations by using NMR techniques clearly reveal that the hemiketal forms are the less dominant ones in solution (except entries 1 and 5 of Table 1), even if they are preferred in the solid state.

The combination of steric repulsions of the substituents at the amine portion and reduced degrees of freedom of the phenoxy substituent are probably the two major reasons for the strong broadening of the NMR signals observed. Since electron-rich 2,4-dimethylphenol is less acidic than phenol (pK_a 10.59[12b]) its acidity is comparable to that of hemiketal hydroxyl groups (pK_a of similar compounds ranges from 9.6 for malvedin-3-glucoside[12c] to 10.4 for α-((β-hydroxyethyl)amino)deoxybenzoines[12d]). In addition, a hindered rotation of the phenoxy moiety seems likely due to different competing hydrogen bonding possibilities.

Crystallisation of the diastereomeric keto and hemiketal form of **12a′/b** occurred in one unit cell, which gives a direct comparison of both competing forms (Figure 3). In the hemiketal form **12a′**, two five-membered ring systems established by hydrogen bonding between hydroxyl oxygen of hemiketal and the amino group (**12a′**, d(O···N) = 2.636(5) Å) as well as the amino substituent and the benzofuran moiety (**12a′**, d(N···O) = 2.654(4) Å) were observed. In addition, a weak π-interaction between the benzofuran moiety and the benzylic amine substituent (d = 3.886 Å) was detected. On the other hand, a significantly higher aberration of the ideal tetrahedral angle (100.49°), leading to an increased ring strain of hemiketal dihydrobenzofuran moiety was found. In contrast, the keto form **12b** exhibits a six-membered ring with hydrogen bonding between the hydroxyl group of the 2,4-dimethylphenol moiety and the amine nitrogen (**12b**, d(O···N) = 2.982(8) Å) as well as a

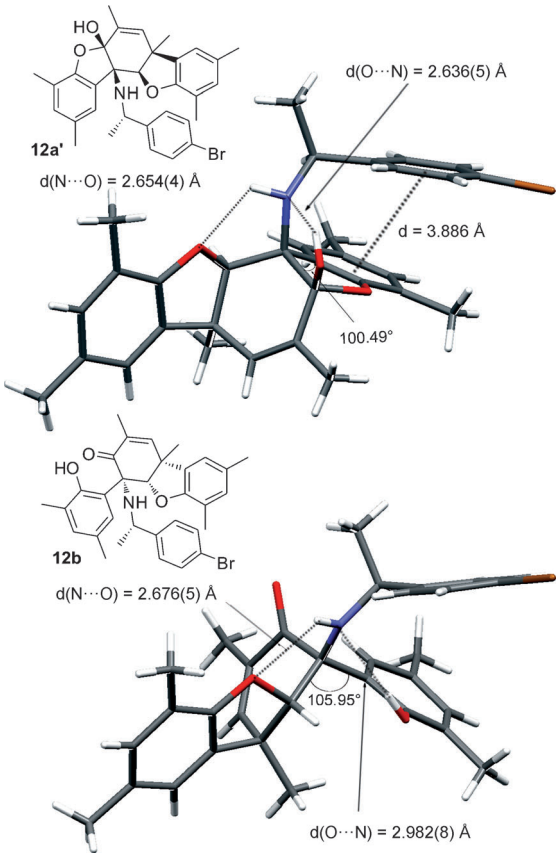


Figure 3. Molecular structures of hemiketal **12a′** (top) and its diastereomeric keto derivative **12b** (bottom) obtained by X-ray analysis. Both compounds were found in same unit cell, but separated here for clarity.

five-membered cycle exhibiting a hydrogen bond, which points from the nitrogen to the adjacent benzofuran moiety (**12b**, d(N···O) = 2.676(5) Å). No π-interactions and a significantly decreased ring strain (angle 105.95°) were identified in derivative **12b**. The hydrogen bonds of hemiketal in **12a′** are shortened in comparison to those of keto form **12b** and are energetically preferred. This might be another directing force for the preferred crystallisation of the hemiketal forms. There are a number of competing electronic and steric effects that are almost balanced and allow a shift of equilibrium by a subtle impact. Consequently, the NMR spectra are remarkable complex. In particular, the NMR spectra of the diastereomeric pair **7a/b** were strongly broadened. In this case an additional repulsion by an *ortho*-methoxy group on the benzylic amine moiety with the surrounding substituents might be responsible for this behaviour. These observations are in agreement with previous studies in which the ring-opening/ring-closure dynamics of related dibenzofuran systems[15] and acyclic substrates[12d] have been studied.

We investigated these dynamic effects and measured ^{1}H NMR spectra of **6a**–**b** and **9a**–**b** at temperatures ranging from −20 to 50 °C. Figure 4 depicts the ^{1}H NMR spectra of derivative **6a′**, in which the temperature was increased in 10 K increments from −20 to 20 °C. This is one of the few

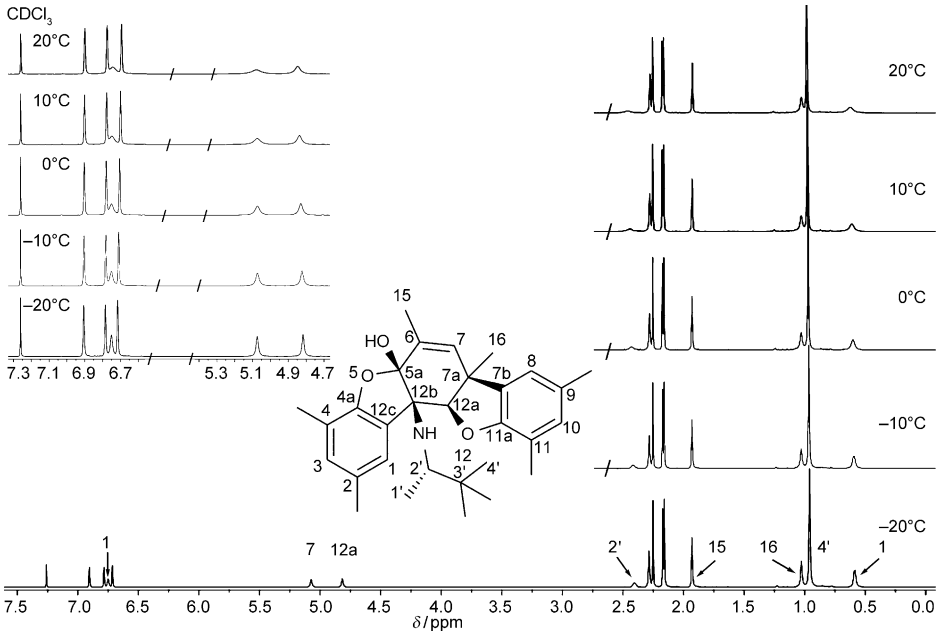


Figure 4. Variable-temperature ^{1}H NMR spectra ($CDCl_3$, −20 to 20 °C) of **6a′** and the assignment of the most important signals. As can be seen by its inspection, even at ambient temperatures a strong signal broadening is clearly observed.

examples in which the hemiketal form was observed exclusively. At higher temperatures, broadening of the signals was observed. Conformational changes in the central cyclohexene ring are translated in broadening of signals of hydrogen atoms at positions 7 and 12a. The portion of the amine moiety closer to the pentacyclic scaffold experiences restricted rotation, probably due to steric hindrance. Thus, signals assigned to protons at positions 1′, 2′, and 1 are close and appear broadened. In contrast, free rotation of the *tert*-butyl substituent causes a sharp signal.

In those cases where both species, hemiketal and ketone, are in equilibrium, the NOESY spectra showed exchange peaks for the corresponding protons of each species (positive and negative signals). Further correlation, observed in HSQC and HMBC experiments, helped to differ among conformer signals. As expected, lowering the temperature led to sharpened signals, even if line broadening is still observable. As indicated by integrating the ^{1}H NMR signals, the concentration of hemiketal form increases successively by lowering the temperature which confirms that they are energetically preferred in the solid state.

Kinetic racemate resolution of *rac*-**2**[16] as a methodology to obtain the enantiomerically enriched dehydrotetramer **2** was also studied. This strategy would pave the way to optically pure polycycles in our diversity-oriented synthesis strategy.[7] Since we expected hydrogen bonding to the approaching amine in the course of the substitution process, a preferential conversion of one enantiomer of **2** might take place. In the field of catalysis, this type of interaction has been successfully used in bis-functionalised substrates possessing hydrogen bonding donor and acceptors.[10] Thus, compound **2** was treated with catalytic amounts of CsF and the amine component (0.4 equiv) at 40 °C and the reaction progress was monitored by RP-HPLC. Unfortunately, the low enantiomeric ratios of approximately 3:1, even at low conversion rates, caused us to stop further studies to achieve optical enrichment by using this approach. Surprisingly, all attempts to rearrange the molecular scaffold of amino derivatives **6–13** failed. Despite the instability of **3** towards acidic media (Scheme 3), the treatment of **6–13** with H_2SO_4 or trifluoromethanesulfonic acid (TfOH) did not induce the formation of spiropentacycle **4**.

Conclusion

The dehydrotetramer (**2**) of 2,4-dimethylphenol has been shown to be a powerful starting material for the synthesis of optically pure polycyclic scaffolds. The amination reaction using suitable enantiomerically pure alkyl and benzylic amines takes place in the course of a nucleophilic substitution of 2,4-dimethylphenoxy leading to diastereomeric products. The diastereomeric pairs can be separated in most cases displaying a dynamic equilibrium between the hemiketal and the α,β-unsaturated cyclohexenone form, in which the latter dominates in solution. These dynamic effects were observed by NMR spectroscopy and in solid state providing a consistent picture. The amination products are stable towards acidic treatment and show a remarkably dynamic behaviour. The equilibrium can be easily shifted. The conversion is accompanied by a significant structural change. Therefore, these unique scaffolds might adapt and bind to a given environment. The biological profile of these compounds will be reported in due course.

Experimental Section

Representative procedure for the synthesis of 6–12: A suspension of **2** (482 mg, 1 mmol), CsF (45.6 mg, 0.3 mmol) and the corresponding amine (2.0 mmol) in CH_3CN (10 mL) was stirred for 3 h at 55 °C. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was adsorbed on silica. Both diastereomers were isolated by subsequent filtration trough a silica gel plug using a mixture of cyclohexane:ethyl acetate (9:1). Resolution of diastereomers was afforded by column chromatography on silica using *n*-hexane/ethyl acetate (20:1) as eluent.

Further details of the synthetic procedures, structural and analytical data can be found in the Supporting Information.

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