Total Synthesis Hot Paper

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Rapid Access to Orthogonally Functionalized Naphthalenes: Application to the Total Synthesis of the Anticancer Agent Chartarin

*Teresa A. Unzner, Adriana S. Grossmann, and Thomas Magauer**

Abstract: *We report the synthesis of orthogonally functionalized naphthalenes from simple, commercially available indanones in four steps. The developed method proceeds through a two-step process that features a thermally induced fragmentation of a cyclopropane indanone with simultaneous 1,2-chloride shift. Migration of the chloride substituent occurs in a regioselective manner to preferentially afford the para-chloronaphthol substitution pattern. The obtained naphthols are versatile building blocks that can be selectively modified and used for the efficient construction of biologically active molecules. This has enabled the total synthesis of the potent anticancer natural product chartarin through a highly convergent retrosynthetic bond disconnection.*

Substituted naphthalenes are common substructural units in many biologically active molecules.[1,2] These include the antiproliferative natural products chartarin (**1**), the aglycon of chartreusin (**2**) and elsamicin,[3] justicidin A (**3**),[4] furomollugin (**4**)[5] and drugs such as the dopamine antagonist nafadotride (**5**)[6] and the nonsteroidal *anti*-inflammatory drug naproxene (Figure 1 a).[7] Traditional strategies for the functionalization of this structural motif hinge on a stepwise approach, that is the electrophilic aromatic substitution of partially substituted naphthalene building blocks.[8] Owing to the inherent low substrate selectivity and the complex substitution pattern found in many natural products, stepwise functionalization from readily available naphthalene precursors is rather inefficient and thus inapplicable for polyfunctionalized molecules. In recent years, methods based on annelation,[2,9] cycloaddition[10] or ring expansion[11] reactions have emerged as possible alternatives to access the bicyclic aromatic system. However, these concepts often require the use of expensive catalysts, involve relatively harsh reaction conditions with inherent lack of functional group compatibility or are dependent on multistep sequences to access the substrates. As a consequence, their application in the synthesis of more complex molecules has remained rather restricted.

As part of our ongoing program to develop practical and scalable methods for the synthesis of polysubstituted, highly functionalized arenes and heteroarenes,[12] we designed a strategy that would allow us to address the current limitations in a highly efficient manner (Figure 1 b). After considering various options, we identified indanone-cyclopropane **A**, readily accessible from a plethora of commercially available, inexpensive indanones via oxidation and cyclopropanation,[13] as the ideal substrate. The envisaged thermally induced disrotatory 2π-electrocyclic ring opening[14] of **A** was expected to be operationally simple on large-scale without requiring additional promoters and requires temporary carbon-halogen bond cleavage. This step produces the benzylallyl cation **B.** Regioselective attack by the chloride anion at the benzylic position affords enone **C** that should spontaneously isomerize to the orthogonally functionalized naphthol **D**. By virtue of the orthogonal functionalization present in **D**, rapid access to selectively modified products would be possible.

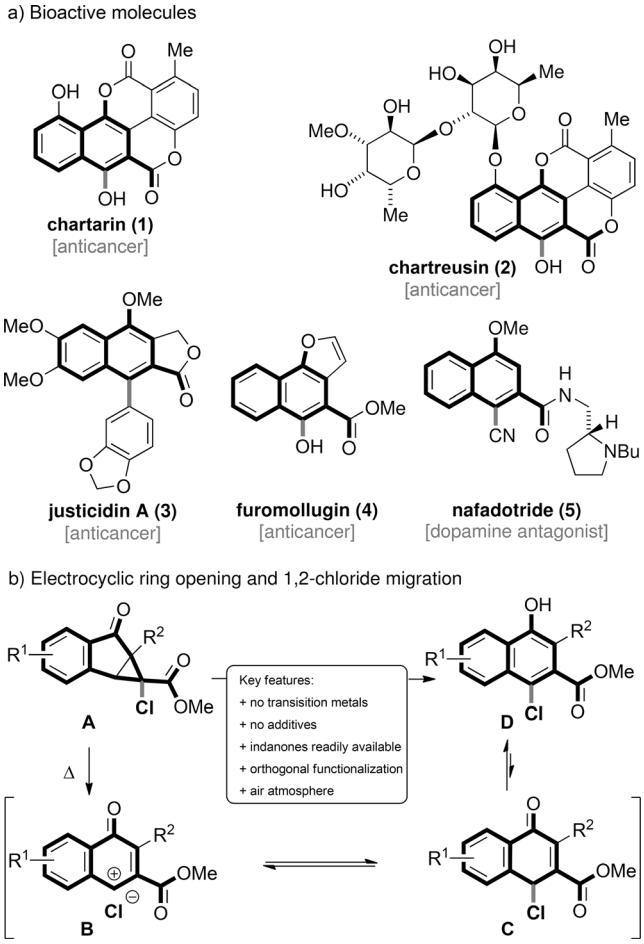

Figure 1. a) Occurrence of naphthalene pharmacophores and b) synthetic design.

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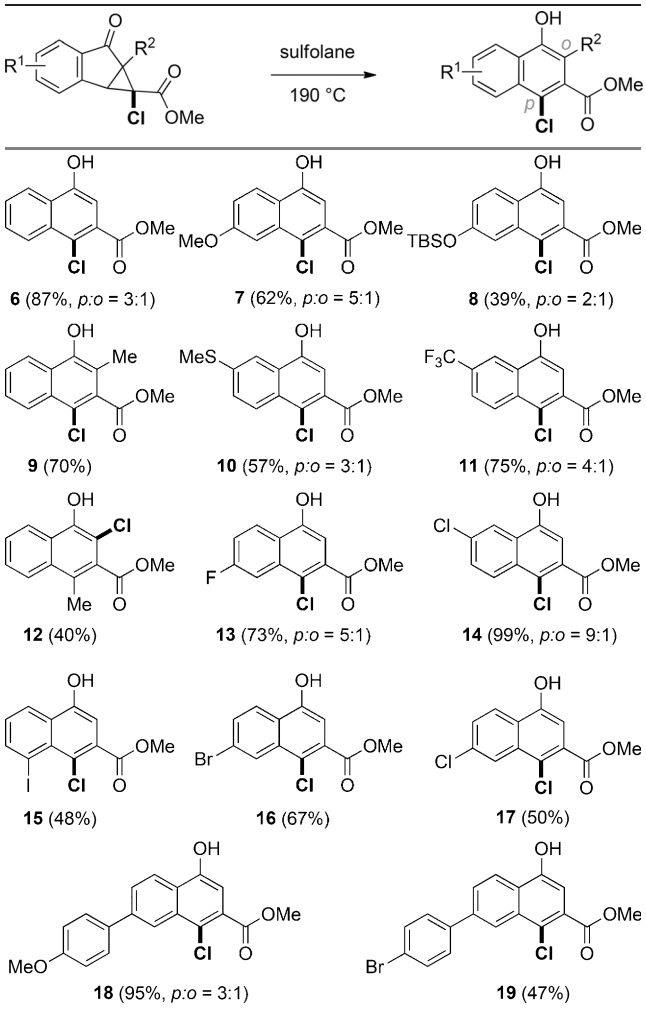
At the outset, we were curious if conditions that were previously developed in our group for the preparation of methyl 3-hydroxybenzoates[12a] could be adapted to this novel substrate class. After a short evaluation of possible reaction conditions, we were pleased to see that the envisaged ring-opening/1,2-migration could be successfully promoted for a panel of compounds upon heating a 0.5 M solution of our substrates in sulfolane at 190 °C (Table 1).

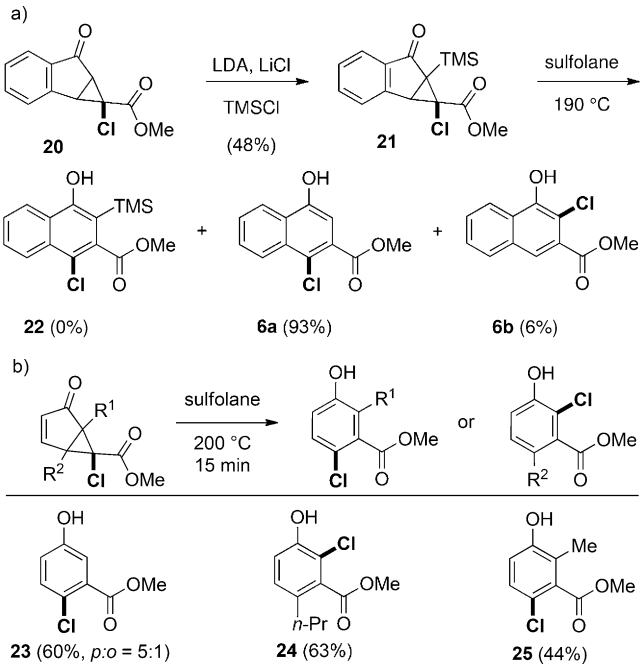
Table 1: Evaluation of substituents in the electrocyclic ring opening to give orthogonally functionalized naphthalenes.[a]



[a] Yield of the isolated product.

At this temperature, the reaction went cleanly to full conversion within less than 30 minutes in most cases. Removal of sulfolane could be best accomplished by repeatedly washing an ethereal (diethyl ether; *tert*-butyl methyl ether) product solution with water. We then investigated the scope of this transformation by varying the substitution pattern of our substrates and evaluated the observed regioselectivity.[15] For the majority of substrates, moderate to high yields were obtained with a strong preference for the formation of the *para*-chloronaphthol substitution pattern. The choice of substituents along the ring junction enabled us to fully direct the migration of the chloride to either the *para*-(compound **9**) or the *ortho*-position (compound **12**). Within this context it is interesting to note that the observed lower yield for **12** might be a result of the inherent substrate preference for the *para*-position. While steric hindrance was expected to affect the regioselectivity to a minor extent, a low degree of delocalization that results in the predominance of the highly stabilized mesomeric resonance structure **B** might account for this observation.

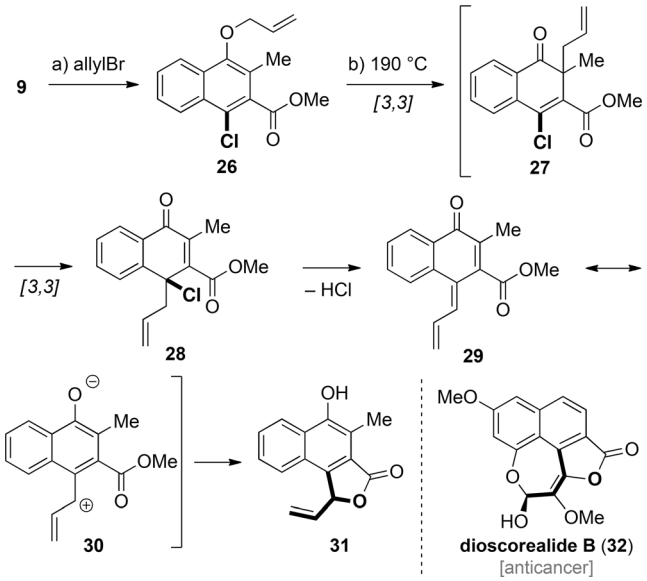
Having established a robust platform for the synthesis of several polyfunctionalized naphthalenes, we evaluated different strategies to further increase the chloride attack at the *para*-position. As illustrated in Scheme 1 a, site-selective



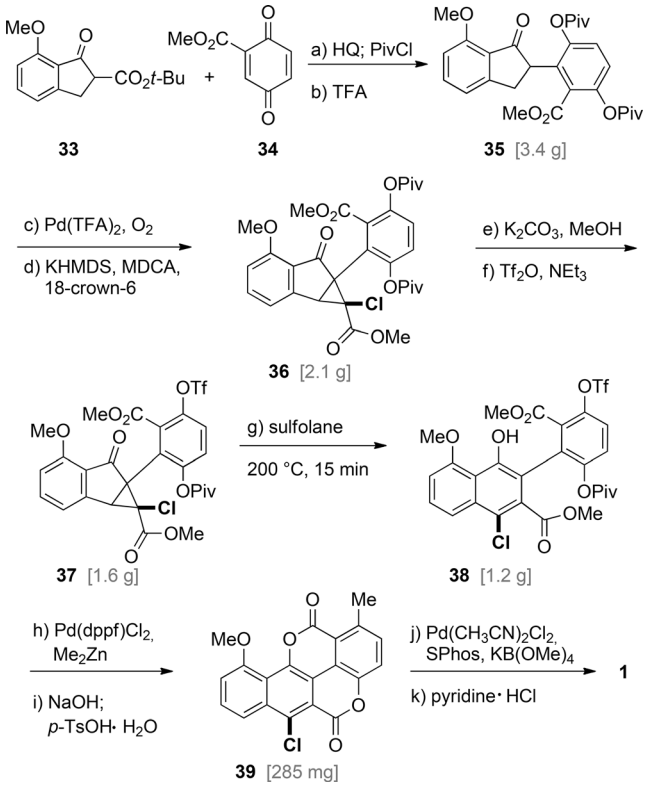
Scheme 1. a) Directed chlorine migration with concomitant carbon-silicon cleavage and b) ring opening of bicyclo[3.1.0]hex-3-en-2-ones to give chlorinated benzoates.

lithiation of the ring opening precursor **20** followed by quenching with trimethylsilyl chloride[16] afforded **21**, which, upon exposure to the standard reaction conditions, was smoothly opened to afford **6a** in excellent yields (93%). This transformation is viewed to proceed via **22**, which undergoes a spontaneous Brook rearrangement at elevated temperatures.[17] The developed transformation was not only limited to bicyclic ring systems, but could also be realized for bicyclo[3.1.0]hex-3-en-2-one substrates as shown in Scheme 1 b.

Having synthesized a library of polysubstituted naphthalenes, we wanted to evaluate the selective modification of our products by taking advantage of the orthogonal reactivity of the hydroxy, chloro and ester substituents. We found out that allyl ether **26** could be converted to tricycle **31** via an unprecedented cascade cyclization (Scheme 2). This sequence is initiated by thermal Claisen rearrangement of **26** to **27**, which then reacts in a subsequent Cope rearrangement to the thermally unstable chloride **28**. Elimination of hydrogen



Scheme 2. One-pot functionalization of naphthyl allyl ether **26** through sequential Claisen–Cope lactonization. Reagents and conditions: a) allylBr, K_2CO_3, acetone, 89%, b) sulfolane, *p*-TsOH·H_2O, 190°C, 15 min, 40%. *p*-Ts = *para*-toluenesulfonyl.



Scheme 3. Application of the ring opening protocol to the total synthesis of chartarin (**1**). Reagents and conditions: a) **33** (1 equiv), **34** (1 equiv), HQ (20 mol%), CH_2Cl_2, −20°C; NEt_3, PivCl, 23°C, 70%; b) TFA, CH_2Cl_2, 23°C, 89%; c) $Pd(TFA)_2$ (20 mol%), 4,5-diazafluoren-9-one (20 mol%), O_2 (1 atm), DMSO, 80°C, 67%, 24% **35**; d) KHMDS, MDCA, 18-crown-6 (10 mol%), THF, −78 to 23°C, 75%; e) K_2CO_3, MeOH, 23°C, 74%; f) Tf_2O, NEt_3, CH_2Cl_2, −78°C to 23°C, 98%; g) sulfolane, 200°C, 15 min, 75%; h) $Pd(dppf)Cl_2$, Me_2Zn, 1,4-dioxane, 95°C, 83%; i) NaOH, CH_2Cl_2, MeOH, 23°C; *p*-TsOH·H_2O, toluene, 80°C, 98%; j) $Pd(CH_3CN)_2Cl_2$ (5 mol%), SPhos (8 mol%), $KB(OMe)_4$, 1,4-dioxane, 90°C, 87%; k) pyridine·HCl, 195°C, 69%. dppf = 1,1′-bis(diphenylphosphino)ferrocene, HQ = hydroquinidine, KHMDS = potassium hexamethyldisilazane, MDCA = methyl dichloroacetate, Piv = pivaloyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

chloride generates a *para*-quinone methide structure **29** and its tautomeric form **30**, respectively. Termination of the sequence could be facilitated by capture of residual water to give a benzylic alcohol that undergoes an acid catalyzed (*p*-TsOH·H_2O) lactonization to afford **31**. Since formation of **31** was also observed under anhydrous conditions, a competing pathway that involves direct attack of the ester might be also operative. The realization of this one-pot cyclization method gives rapid access to annulated naphthalene lactones, an important structural motif that is also part of dioscorealide B (**32**).[18]

An additional remarkable feature of the developed ring-expansion reaction is the possibility to design powerful retrosynthetic bond disconnections for the construction of highly substituted, sterically hindered biaryl compounds. The first application of this strategy could be realized in the convergent total synthesis of the potent anticancer natural product chartarin (**1**).[3b] We began our synthesis with the coupling of indanone **33**, derived from commercially available 7-methoxy-1-indanone in one synthetic operation, to the known *para*-quinone **34** (Scheme 3).[19] For the conjugate addition of **33** to **34,** we relied on a previously reported protocol by Jørgensen.[20] Thus, in the presence of catalytic amounts of hydroquinidine (20 mol%), immediate consumption of the equimolar mixture of reactants occurred. Trapping of the formed hydroquinone as its bis-pivalate ester prevented oxidation to the quinone, and subsequent addition of trifluoroacetic acid promoted decarboxylation of the *tert*-butyl ester to afford the 2-arylated indanone **35** in good overall yield on gram scale. Next, oxidation of **36** to the indenone could be accomplished using Stahl's palladium-catalyzed aerobic dehydrogenation conditions.[21] In order to overcome the low reactivity of the 2-substituted indenone in the following cyclopropanation reaction, we had to modify the standard reaction conditions. Replacement of lithium hexamethyldisilazane (LHMDS) by its potassium derivative KHMDS in the presence of 18-crown-6 allowed us to improve the initial low yield of **36** to 75%. Sequential treatment of **36** with methanolic potassium carbonate and then triflic anhydride provided **37**. Having prepared sufficient amounts of the crucial intermediate (1.6 g), we turned our attention to the key-step of the synthesis. Heating a solution of triflate **37** in sulfolane at 200°C for 15 min induced the desired ring opening reaction and led to clean conversion to the biaryl intermediate **38** (75%, 1.2 g). For the installation of the methyl group, a site-selective coupling of the triflate had to be developed. Careful experimentation revealed that, upon exposure of **38** to an excess of dimethyl zinc in the presence of $Pd(dppf)Cl_2$ at 95°C for 1 h, the chloride was left unreacted and exclusive insertion at the triflate occurred.[22]

Lactone formation with loss of the biaryl axis was promoted upon hydrolysis of the remaining pivalate

(NaOH, MeOH) and acid catalyzed (p-TsOH·H_2O) ring closure at elevated temperature (toluene, 80 °C) gave **39**. Substitution of the chloride with a hydroxyl group was initially investigated with a model substrate that was lacking the methoxy substituent (see Supporting Information for further details). To our surprise, this seemingly trivial coupling reaction was not successful under a variety of reaction conditions[23] and, in most cases, only dehalogenation of the starting material was observed. Fortunately, when a solution of the more electron rich naphthalene **39** in 1,4-dioxane (0.05 M) was exposed to potassium tetramethoxyborate in the presence of bis(acetonitrile)dichloropalladium(II) (5 mol %) and SPhos (8 mol %) at 90 °C for 3 h, efficient incorporation of the desired methoxy group occurred (87 %).[24] For the completion of the synthesis, simultaneous removal of both methyl substituents was accomplished by treatment of **39** with pyridine hydrochloride at elevated temperature (195 °C) for 16 h. Chartarin (**1**) crystallized from methanol as a yellow-brownish powder whose spectroscopic data (^{1}H and ^{13}C NMR, mp, HRMS) were in full agreement with those reported for the naturally occurring substance.[3b,25]

In conclusion, we have developed an efficient and practical ring opening/1,2-migration transformation for the synthesis of orthogonally functionalized naphthalenes. The reaction is operationally simple, does not require any additives, occurs in a regioselective manner with a strong preference for the *para*-chloronaphthol substitution pattern and enables novel, powerful retrosynthetic bond disconnections. A translation of this method to natural product synthesis was realized for the preparation of the potent anticancer agent chartarin (**1**). The developed route can be conducted on gram scale, provides efficient access to the highly substituted, polycyclic carbon framework and enables rapid diversification by standard transformations. Further applications of this concept in the synthesis of complex naphthalene containing molecules are currently underway in our laboratories.

Acknowledgements

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Keywords: arenes · naphthalenes · natural products · ring expansion · total synthesis

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Communications

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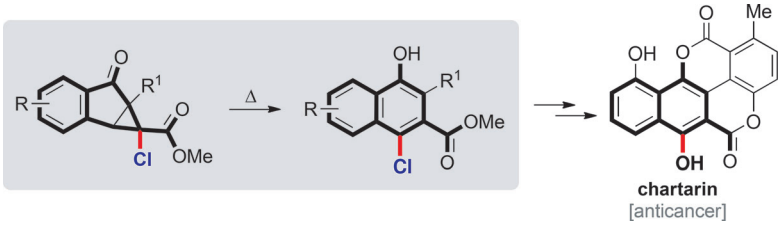

Substituted naphthalenes: Orthogonally functionalized naphthalenes were synthesized from commercially available indanones in four steps. The developed method proceeds through the thermally induced fragmentation of cyclopropane indanones and involves a regioselective 1,2-chloride shift. This transformation enables the synthesis of the anticancer agent chartarin.