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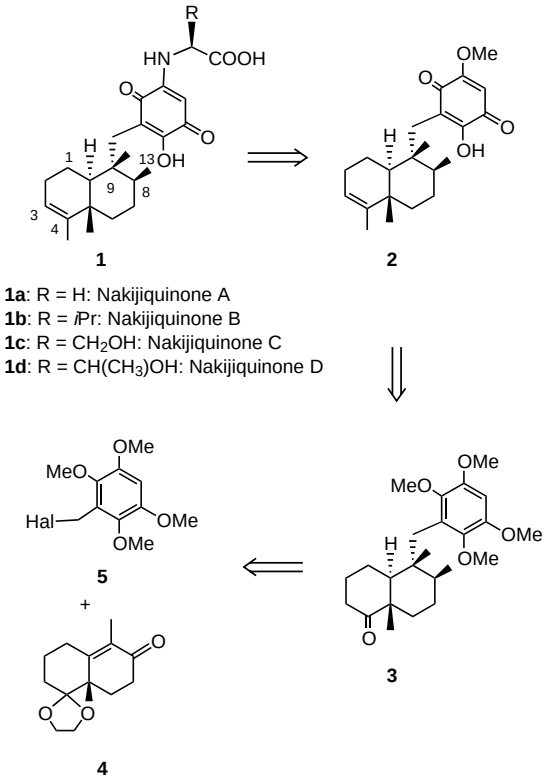
Asymmetric Synthesis of the Nakijiquinones—Selective Inhibitors of the Her-2/Neu Protooncogene**

Petra Stahl and Herbert Waldmann*

Extracellular growth-promoting signals are recognized in many cases by transmembrane receptors with tyrosine kinase activity. These proteins trigger numerous intracellular signalling cascades by which cell growth, proliferation, and other genetic programs are regulated.[1] Dysregulation of these signal sequences may contribute to or cause many diseases. For instance, enhanced activity of receptor tyrosine kinases can promote tumor growth and has been implicated in carcinogenesis.[2] A particularly relevant example is the Her-2/Neu-protooncogene (also called erbB-2). This receptor is vastly overexpressed in about 30% of primary breast, ovary, and gastric carcinomas.[1, 3, 4] Amplification is closely correlated with the clinical behavior of these neoplasms, such that tumors with Her-2 amplification are more agressive and associated with reduced patient survival. Therefore, compounds that can selectively block Her-2 activity are of paramount importance for the development of new anticancer drugs;[1, 2, 5] a monoclonal antibody against Her-2 has already been introduced by Genentech into the clinic as a new revolutionary treatment for breast cancer. In addition, such drugs are likely to be useful in dissecting signalling pathways.[2, 6, 7] Until today only a few natural products with intrinsic tyrosine kinase inhibiting activity per se were isolated and, in particular, a natural product that inhibits Her-2 has not been synthesized.[2, 6] Recently, however, the nakijiquinones **1a – d** (see Scheme 1) were identified as selective inhibitors of the Her-2/Neu kinase, displaying pronounced cytotoxicity against L 1210 murine leukemia cells and KB human epidermoid carcinoma cells.[8] We now disclose the first enantioselective total synthesis of the nakijiquinones.

The nakijiquinones embody three basic structural elements, an amino acid, a central *p*-quinoid unit, and a diterpenoid system. To reach a high degree of convergency, the nakijiquinones were first, dissected in a retrosynthetic sense into isospongiaquinone (**2**), an interesting natural product in its own right[9] and an amino acid that can be introduced in the last step by conjugate addition to the vinylogous methyl ester present[8] (Scheme 1). It was further planned to generate the selectively functionalized quinoid system by oxidation of a tetramethoxy-substituted aromatic precursor **3** to a 1,4-dicarbonyl compound and subsequent selective saponification



Scheme 1. Retrosynthetic analysis of the nakijiquinones **1**.

[*] Prof. H. Waldmann, Dipl.-Chem. P. Stahl
Max-Planck-Institut für molekulare Physiologie
Otto-Hahn-Strasse 11, D-44227 Dortmund (Germany)
Fax: (+49) 231-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de

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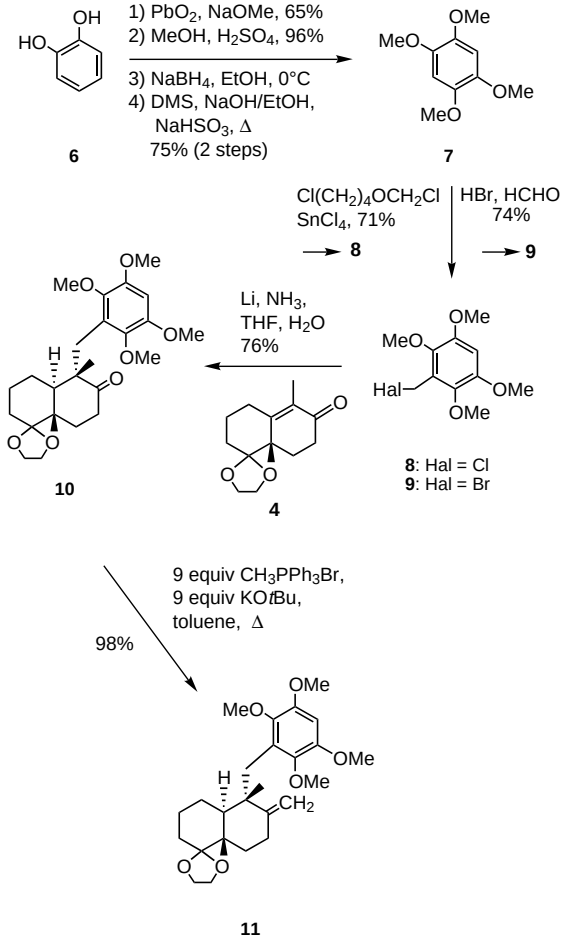
of one of the two vinylogous methyl esters generated thereby. For the synthesis of the diterpene structure and its coupling with the alkoxy-substituted aromatic compound, we resorted to the reductive alkylation of α,β-unsaturated Wieland–Miescher type enone **4** with a benzyl halide **5**. This strategy had already proven to be useful in the construction of related natural products.[10] Finally, we envisaged generating the endocyclic 3,4-alkene by olefination of a ketone at C-4 and subsequent isomerization of the generated exocyclic double bond. It was also planned to introduce the C-13 methyl group by an olefination/reduction sequence of an intermediary generated ketone.

Benzyl halides **8** and **9** were prepared from catechol (**6**) in five-step sequences as shown in Scheme 2. To this end, **6** was oxidized to the corresponding *ortho*-quinone, which rapidly added NaOMe. Subsequent reoxidation led once again to an



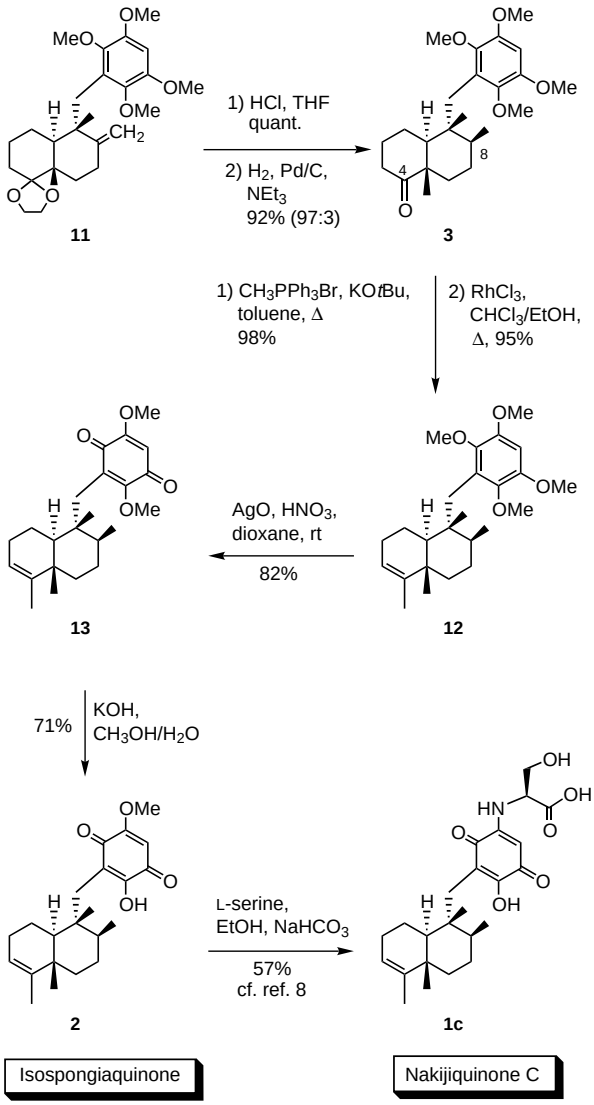
Scheme 2. Synthesis of tetramethoxyaryl intermediates **8** and **9.**

ortho-quinone that was rearranged under acidic conditions to the corresponding *para*-quinoid compound.[11] The keto groups were then reduced, and the resulting 1,4-diphenol was O-methylated to give tetramethoxybenzene **7**. Compound **7** was converted efficiently in one-step reactions into benzyl halides **8** and **9**. Wieland–Miescher type ketone **4** required for the critical reductive coupling step was synthesized by Robinson-annelation and subsequent selective monoprotection by transacetalization.[12] In the decisive coupling of benzyl halides **8** and **9** and enone **4** the reaction conditions reported for related structures could not be employed successfully. Benzyl chloride **8** did not react at all with the radical anion generated from enone **4** by treatment with lithium in ammonia. However, a yield of 76% was obtained reproducibly if a solution of twelve equivalents of benzyl bromide **9** in THF was added rapidly at $-78\,^{\circ}C$ to a preformed solution of the radical anion in NH_3/THF (final ratio NH_3:THF = 1.0:0.7) and subsequent refluxing at $-33\,^{\circ}C$ for 2 h. The radical anion was generated by adding a solution of enone **4** in THF/water (1:0.018) at $-78\,^{\circ}C$ to 30 equivalents of Li/NH_3 followed by refluxing for 45 min and recooling to $-78\,^{\circ}C$.

The conversion of the keto group present in **10** into the corresponding *exo*-methylene compound **11** was unexpectedly difficult. Several established methylenation reagents such as the Tebbe reagent[13] and [Cp_2TiMe_2][14] failed completely, and under various conditions the Wittig reaction either yielded no product at all or only an unsatisfactory low amount of the desired olefin. Finally, the use of nine equivalents of H_3CPPh_3Br together with nine equivalents of KO*t*Bu in refluxing toluene[15] turned out to be the method of choice, yielding the exocyclic olefin **11** in nearly quantitative yield. Disappointingly, reduction of the olefin **11** with PtO_2 proceeded without recordable stereoselectivity. We felt that this might be due to an unfavourable conformation of the bicyclic system and envisaged that removal of the acetal protecting group might improve the situation. This turned out to be the case. After cleavage of the acetal, the stereoselectivity of the reduction with PtO_2 in CH_2Cl_2 was raised to 80:20, and use of Pd/C as catalyst in NEt_3 as solvent yielded ketone **3** in 92% as a 97:3 mixture of epimers at C-8 (Scheme 3). As planned, the ketone at C-4 was converted in very high overall yield to endocyclic alkene **12** by olefination (for which the conditions described above once more proved to be very efficient), and subsequent rhodium-catalyzed isomerization of the exocyclic to the endocyclic double bond.

The next two steps in the synthetic sequence, that is the oxidation of the tetramethoxyphenyl ring to the *para*-quinoid system and the subsequent selective removal of the correct *O*-methyl group posed major problems. Oxidation of the aromatic system was initially attempted by applying CrO_3 or cerium ammonium nitrate which had proven to be useful reagents in related studies.[10c,d, 16] However, oxidized intermediate **13** was formed only in low yield or not at all. After substantial variation of the reaction conditions, finally the use of AgO and catalytic amounts of HNO_3 at room temperature in dioxane as solvent evolved as the method of choice.[17] Under these conditions *p*-diketone **13** and the regioisomeric *o*-diketone were obtained in a total yield of 82% as an isomeric mixture. The undesired *o*-diketone was readily rearranged to **13** by treatment with acid.

Selective removal of the correct *O*-methyl group was attempted by a variety of methods. In particular, the use of various different Lewis acids (BCl_3, BBr_3, $AlCl_3$, $BF_3 \cdot OEt_2$/EtSH, $HClO_4$ and trimethylsilyl iodide) was unsuccessful and led to decomposition of the starting material. Also, attempts to cleave a methyl ether before the oxidation did not succeed and resulted exclusively in Lewis acid mediated rearrangements of the terpene backbone. Finally, treatment of vinyl-



Scheme 3. Synthesis of isospongiaquinone (**2**) and nakijiquinone C (**1c**).

ogous diester **13** with KOH in aqueous methanol led to saponification of the correct methoxy group and gave rise to the desired product **2** in 71% yield. Presumably, the reaction proceeds by conjugate addition of hydroxide to one of the vinylogous esters and elimination of methanol. Compound **2** is identical with isospongiaquinone, a natural product isolated from *Stelospongia conulata*.[9] Specific rotation, IR and NMR spectroscopic data of synthetic **2** were in full accord with the data reported for the natural product, thereby proving the absolute configuration of the synthesized compound.[18]

Isospongiaquinone (**2**) may be employed as a central intermediate for the synthesis of all nakijiquinones. Treatment of this compound with amino acids in ethanol in the presence of $NaHCO_3$ results in the conversion of the remaining vinylogous ester in **2** into the corresponding vinylogous amide.[8] We have verified this finding and converted isospongioquinone (**2**) into nakijiquinone C (**1c**) by treatment with L-serine (Scheme 3). The IR and NMR spectroscopic data recorded for the synthetic sample completely matched the data published for the natural product.[19] Unexpectedly, however, synthetic nakijiquinone **1c** displayed a positive specific rotation, whereas for the compound isolated from natural sources a negative rotation was reported.[8] But as described above, the IR and NMR data of **1c** are in full accord with the published values for natural nakijiquinone C, and the diastereomer formed from isospongiaquinone and D-serine shows a markedly different specific rotation.[8] Thus, in the conversion of intermediate **2** to target compound **1c** an undesired diastereomer cannot have been formed. In addition, all data (including the specific rotation) recorded for isospongiaquinone synthesized as shown in Scheme 3, are in full accord with the values published for this natural product. Thus, if the absolute configuration of synthetic **2** is correct, nakijiquinone C (**1c**) must have been formed with the correct absolute configuration, as well.[20]

In conclusion we have developed the first enantioselective access to the nakijiquinones, the only natural products known to selectively inhibit the Her-2/Neu protooncogene. This synthetic route should give access to various analogues of these interesting and biologically relevant kinase inhibitors. Thereby new opportunities for the development of selective inhibitors of the Her-2/Neu receptor tyrosine kinase and for the study of the signaling pathways influenced by this enzyme may be opened up.

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[18] Analytical data for **2**: M.p. 1359 °C (hexene) [ref. [9]: m.p. 135.5–1369 °C (hexene)]; IR (KBr): $\tilde{\nu}$ = 3337, 1645, 1609, 1460, 1380, 1320, 1234, 1209, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (br. s, 1H), 5.85 (s, 1H), 5.12 (br. s, 1H), 3.84 (s, 3H), 2.63 (d, 1H, J = 13.7 Hz), 2.49 (d, 1H, J = 13.7 Hz), 2.06–1.97 (m, 1H), 1.92–1.83 (m, 1H), 1.63 (dt, 1H, J = 12.7, 3.3 Hz), 1.54 (s, 3H), 1.47–1.04 (m, 6H), 1.00 (s, 3H), 0.97 (d, 3H, J = 6.1 Hz), 0.92–0.88 (m, 1H), 0.84 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 182.4, 182.1, 161.8, 153.2, 144.0, 120.9, 117.6, 102.0, 56.8, 47.8, 43.1, 38.5, 37.8, 36.0, 32.3, 27.9, 27.0, 20.2, 19.8, 18.2, 17.7, 17.4; MS: (EI, 70 eV, 858 C): m/z: 358 [M^+], 281, 236, 191, 168; HRMS (EI) calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2131; $[\alpha]_D^{20}$ = +62.4 (c = 0.25, $CHCl_3$) [ref. [9] $[\alpha]_D^{20}$ = +64.8 (c = 1, $CHCl_3$)].

[19] Analytical data for **1c**: IR (KBr): $\tilde{\nu}$ = 3417, 1679, 1650, 1597, 1556, 1391, 1209 cm^{-1}; ^1H NMR (500 MHz, [D_6]DMSO): δ = 7.16 (d, 1H, J = 7.3 Hz), 5.34 (s, 1H), 5.06 (s, 1H), 4.21 (m, 1H), 3.82 (m, 1H), 3.78 (m, 1H), 2.43 (d, 1H, J = 13.5 Hz), 2.32 (d, 1H, J = 13.5 Hz), 2.01–1.89 (m, 3H), 1.54 (m, 1H), 1.47 (s, 3H), 1.39–1.15 (m, 4H), 1.03–0.98 (m, 2H), 0.93 (s, 3H), 0.89 (d, 3H, J = 7.3), 0.77 (s, 3H); MS: (–FAB, diethanolamine matrix): m/z: 432 [M+H], $[\alpha]_D^{20}$ = +62 (c = 0.13, EtOH) [ref. [8] ($[\alpha]_D^{20}$ = –73° (c = 0.03, EtOH)].

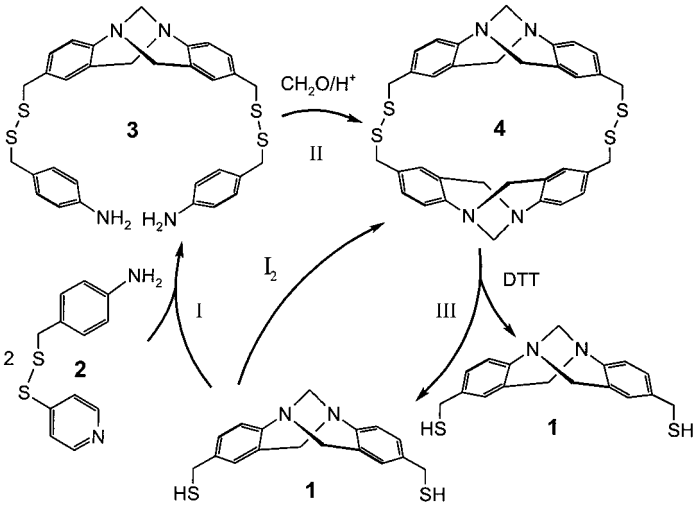
[20] The direction of the specific rotation reported for nakijiquinone C isolated from natural sources is indeed incorrect. Reexamination of the original sample yielded a value of $[\alpha]_D^{20}$ = +138° (c = 0.1, EtOH): Prof. Jun'ichi Kobayashi, Hokkaido University, Sapporo; personal communication.

Stepwise Replication of a Tröger's Base Analogue**

Braja G. Bag and Günter von Kiedrowski*

Molecular replication lies in the heart of biological systems. In its minimal representation, molecular replication is the ability of a molecule to form a copy of itself with transfer of constitutional information. In recent years, the phenomenon has been studied with various chemical model systems based on oligonucleotides,[1] peptides,[2] and other synthetic supramolecular systems,[3] aiming to gain an improved understanding of prebiotic replication.[4] A common problem of these template-mediated catalytic systems, regardless of whether they are autocatalytic or cross-catalytic, is product inhibition leading to parabolic amplification. Recently, an exponential amplification procedure based on oligonucleotides immobilized on a solid support was reported by Luther et. al.[5] Here we report a new scheme for stepwise replication that is based on a Tröger's base analogue and utilizes macrocyclization and covalent templating.

Tröger's base with its rigid V-shaped geometry has become attractive in recent years in the general area of supramolecular chemistry.[6] For the design of a novel replicating system based on a Tröger's base analogue, we realized that a thiol–disulfide exchange reaction[7] could be integrated with the formation of Tröger's base.[6b] Molecular modeling using the PCMODEL[8] program supported the geometric feasibility of the "dimeric" macrocyclic structure **4** (see Scheme 1). We chose compound **1**, which has two appended thiol groups at the 2- and 8-methyl groups of Tröger's base, as a template. It occurred to us that reaction of **1** with **2** will produce **3** by a thiol–disulfide exchange reaction (Scheme 1). Intramolecular condensation of the two aniline units of **3** will produce **4**. Reductive cleavage of the disulfide linkages of **4** will generate a replica of **1** along with the parent template.



Scheme 1. Stepwise replication of Tröger's base analogue **1** by macrocyclization and covalent templating.

We have previously reported the synthesis of compound **1**.[9] Indirect evidence for the practicability of the replication Scheme came from the fact that oxidation of **1** with iodine[10] under high dilution conditions in THF afforded **4** as the major product detectable by HPLC (Table 1). Treatment of a solution of **1** in chloroform with **2** in the presence of *p*-toluenesulfonic acid afforded **3** in quantitative yield. The insoluble byproduct 4-thiopyridone was separated by filtration and the bis-amine **3** was directly used for the macrocyclization. Condensation of **3** with formalin in chloroform/

[*] Prof. Dr. G. von Kiedrowski, Dr. B. G. Bag
Lehrstuhl für Organische Chemie I – Bioorganische Chemie
der Universität
Universitätsstrasse 150, D 44780 Bochum (Germany)
Fax: (+49) 234-32-14355
E-mail: kiedro@ernie.orch.ruhr-uni-bochum.de

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