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Setup of 4-Prenylated Quinolines through Suzuki-Miyaura Coupling for the Synthesis of Aurachins A and B

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Dedicated to Prof. Dr. Dr. h.c. mult. Gerhard Bringmann on the occasion of his 70th birthday

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Abstract: A polyprenyl side chain could be introduced into the heterocyclic quinoline moiety through Suzuki-Miyaura coupling of the corresponding quinoline-*N*-oxide with a polyprenyl boronic acid. This tool could be utilized for the synthesis of the natural product Aurachin B from the myxobacterium *Stigmatella aurantiaca*. This prenylated quinoline could then be transformed into the related Aurachin A through an epoxidation-ring opening cascade.

Keywords: Aurachins; Suzuki-Miyaura coupling; Prenylated quinolines; Total synthesis; Natural product

Introduction

Aurachins A–P are a family of 12 secondary metabolites produced by the myxobacterium *Stigmatella aurantiaca* strain Sg a15 and possess numerous bioactivities, such as anti-bacterial, anti-fungal and anti-plasmodial properties.[1] Furthermore, these isoprenoid quinoline alkaloids are potent inhibitors of mitochondrial respiration by targeting the cytochrome *b*6/*f*-complex, as well as the complexes I and III in the respiratory chain.[2] Other quinoline derivatives – as well with extended side chains – are of growing pharmaceutical interest.[3] Aurachins A (**4**), B (**3**) and C (**2**) were identified as major compounds produced by the strain whereas Aurachin D (**1**) as well as E–P are minor ones. However, in a plausible biosynthesis pathway for Aurachins which was deduced from feeding studies, **1** was identified as the biogenetic parent compound.[4] The puzzle of the modular Aurachin biosynthesis in *Stigmatella aurantiaca* involving polyketide synthases (*AuaB-E*), a prenyl transferase (*AuaA*) as well as a Rieske oxygenase (*AuaF*) for *N*-oxidation was extensively studied.[5] As outlined in scheme 1, the biosynthesis starts with anthranilic acid to generate the 4-quinolone **1** as the first Aurachin (originally named "D") in this sequence. Biological *N*-oxidation then yields Aurachin C (**2**) as *N*-hydroxy-4-quinolone which can be converted into other Aurachins of this "C-type" in further biosynthetic steps.

Furthermore, a side chain migration gives rise to the "A-type" represented by Aurachin B (**3**) as 3-hydroxyquinoline-*N*-oxide and Aurachin A (**4**) is obtained thereof by side chain expoxidation and ring opening (by *AuaI, J*).[6] For the side chain migration

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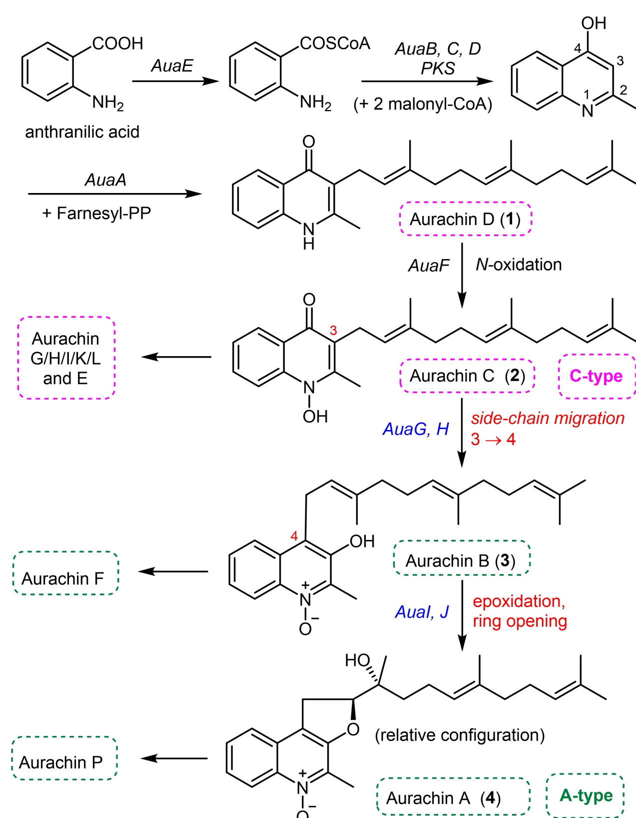
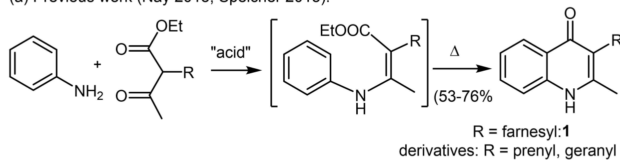
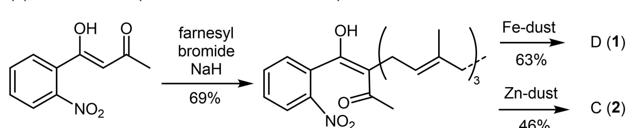


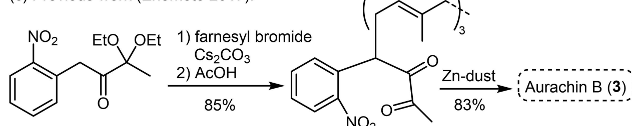
Scheme 1. Proposed biosynthesis of the Aurachin family produced by *Stigmatella aurantiaca* (AuaA-J: enzymes involved; PKS: polyketide synthase III).

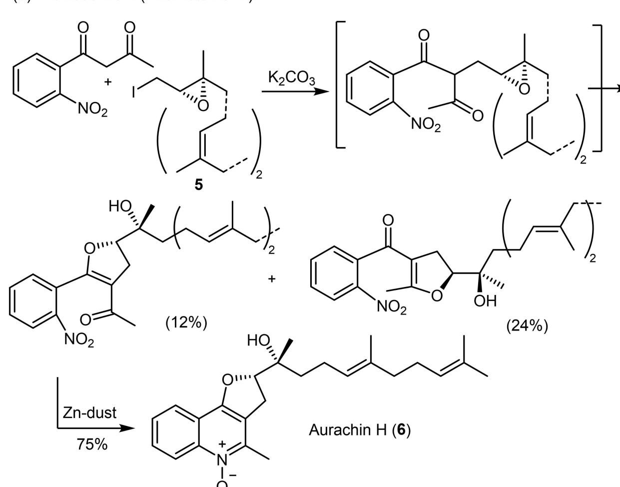
(position 3→4), a 2,3-epoxidation followed by a pinacol type rearrangement (by AuaG, H) was first postulated,[7] but an alternative mechanism through a retro-[2,3]-Wittig rearrangement was also discussed.[8] Some more modified Aurachin derivatives could be isolated by fermentation experiments as well as from different *Rhodococcus* or *Streptomyces* strains.[9]

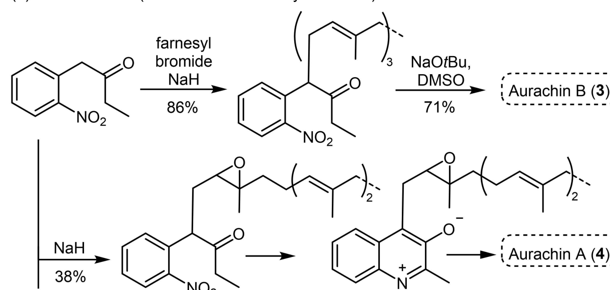
Reports on total syntheses of Aurachins started in 2013 when Nay's and our group independently published quite similar syntheses of Aurachin D (**1**) and derivatives with geranyl or prenyl side chain.[10] The method is based on the Conrad-Limpach cyclization[11] starting with aniline and the appropriate α-substituted ethyl acetoacetate (Scheme 2a). In 2014, Enomoto and Shimizu obtained Aurachin D (**1**) and C (**2**) by reductive cyclization of a δ-nitro-1,3-diketone (as enol) obtained from *o*-(acetylacetonato) nitrobenzene.[12] Depending on the reductive power, the nitro group was reduced to the corresponding amine or hydroxylamine, respectively, before cyclization through enamine formation (Scheme 2b). In 2017, the same group was able to synthesize Aurachin B (**3**) through a similar strategy (Scheme 2c) but considering the different position of the farnesyl side chain (type C versus type A).[13] Furthermore, they obtained Aurachin











Scheme 2. Previous syntheses of Aurachins.

H (**6**) which can be considered as the type C analogue of Aurachin A (**4**), though in low yield caused by a concomitant cyclization. The epoxide in the side chain fragment **5** was introduced regioselectively and enantioselectively through a Sharpless-Katsuki protocol leading finally to (2'*S*,3'*R*)-**6** (Scheme 2d). It should be noted that the absolute configuration of the natural Aurachins A (**4**) and H (**6**) were not reported. Finally, in 2017 Yokoshima and Fukuyama reported on an

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alternative synthesis for Aurachin B (**3**) and the first synthesis for Aurachin A (**4**).[14] Again, the nitro group served as precursor for cyclization which now, however, was envisaged as aldol addition to the nitro functionality (Scheme 2e). For Aurachin A (**4**) the epoxide was preliminary introduced in racemic manner allowing cyclization to the fused furane ring. It should be noteworthy that direct transformation of **3** to **4** through an intermediate oxirane was not possible because the lack of regioselectivity for the epoxidation. In the biogenetic process however, this is realized through enzymatic control (compare Scheme 1).

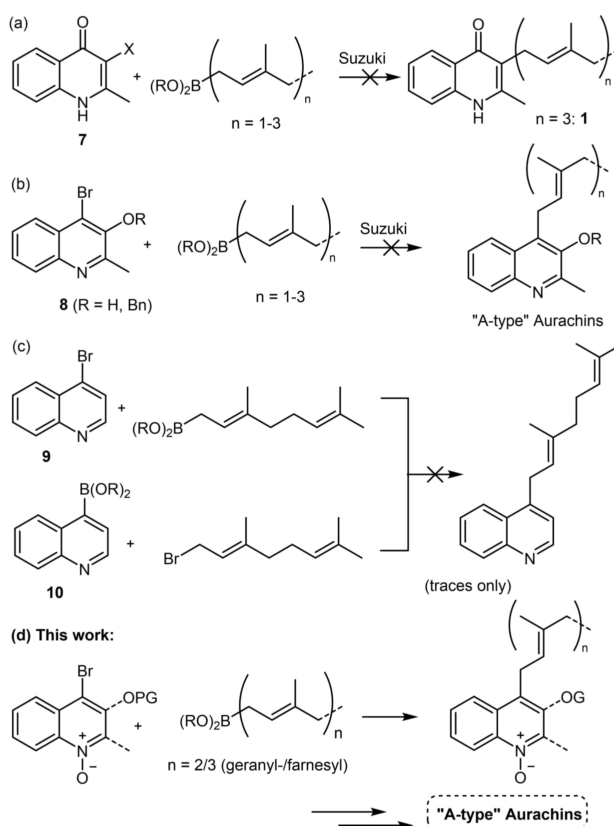
Results and Discussion

As a common principle of the foregoing syntheses, the cyclization to different quinoline type heterocycles is performed with precursors already bearing the polyprenyl type side chain. An obvious and even more flexible strategy could be the cross-coupling of a ready-made quinoline heterocycle and the envisaged side chain. Already in the case of our synthesis of the "C-type" Aurachin D (**1**) (compare Scheme 2a) we failed using a Suzuki-Miyaura coupling between a 3-halo-4-quinolone **7** and an allylic boronic acid (or ester) like prenyl, geranyl or farnesyl (Scheme 3a).[15] Our first attempts to obtain "A-type" Aurachins starting with 4-halo-3-hydroxyquinolines **8** likewise failed (Scheme 3b).

To simplify the target reaction, we switched to Suzuki-Miyaura coupling between 4-bromoquinoline (**9**) and geranyl boronic acid/ester or vice versa a quinoline-4-boronic acid/ester **10** and geranyl bromide, which both failed or had very low yield using different cross-coupling conditions (Scheme 3c). Geranyl compounds are more stable (compared to prenyl) and cheaper than farnesyl and therefore used, in general, for further model reactions.

To our surprise, Suzuki-Miyaura coupling of haloquinolines with allyl/polyprenyl-type boronic acids were not discussed in literature yet. 3/4-Haloquinolines were successfully reacted with aryl-, hetaryl-, vinyl or even cyclopropyl boronic esters.[16] On the other hand, allyl-/polyprenyl boronic acids were successfully coupled only with simple haloarenes.[17]

Regarding the presence of the *N*-oxide functionality in Aurachins A and B, which should be introduced at early stage to overcome selectivity confusion (*N*-versus side chain epoxidation, see above), we focussed now on the ability of quinoline-*N*-oxides for Suzuki-Miyaura coupling with prenyl type boronic acids (Scheme 3d). The significant change of electronic and reactivity properties by *N*-oxidation is well known and extensively studied for pyridine versus pyridine-*N*-oxide.[18] The same effects are reported for quinoline-*N*-oxides.[19] However, Suzuki-Miyaura couplings with haloquinoline-*N*-oxides are rare[20] and again, no examples for coupling with prenyl type boronic acids are reported. For this reason, we started systematic studies on this area.



Scheme 3. Aurachins through Suzuki-Miyaura coupling of quinolines and prenyl type compounds.

The syntheses of all starting materials (quinoline as well as prenyl derivatives) are described in the supporting information section. First, we thoroughly tried again to optimize the Suzuki-Miyaura coupling conditions with simple 4-haloquinolines **9 a/b** and geranyl boronic acid **11**. Whereas the bromo compound **9 a** completely failed, the iodoquinoline **9 b** gave very low yields for the geranyl quinoline **12** (Scheme 4a). Switching to 4-haloquinoline-*N*-oxides **13 a/b**, coupling with **11** resulted in moderate yields (Scheme 4b). The next step was to introduce the 2-methyl group into the target molecule. 4-Halo-2-methylquinoline-*N*-oxides **15 a/b** were reacted with **11** to obtain the 4-geranyl-2-methylquinoline-*N*-oxide (**16**) (Scheme 4c). Whereas the bromo compound **15 a** gave enhanced results, the iodo compound **15 b** proved to be even more unstable than **9 b/13 b** resulting in decomposition rather than Suzuki-Miyaura coupling. For this reason, iodoquinolines were no longer considered.

With respect to the target molecule Aurachin B (**3**) introduction of the 3-hydroxyl group was the next task.

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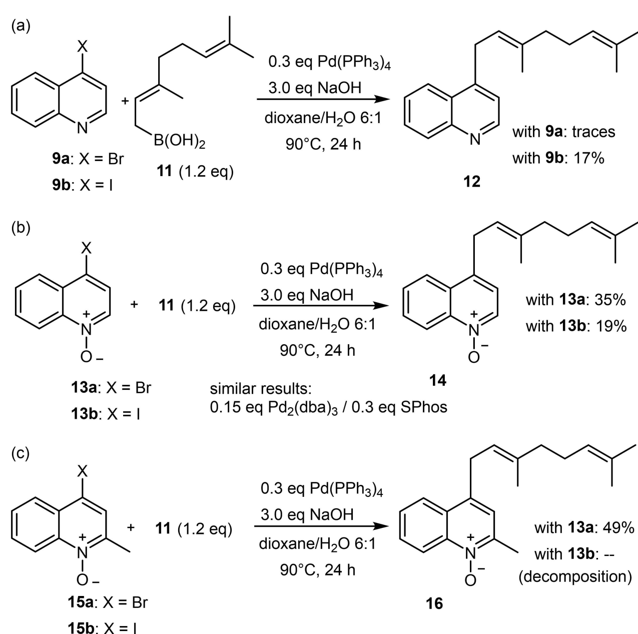
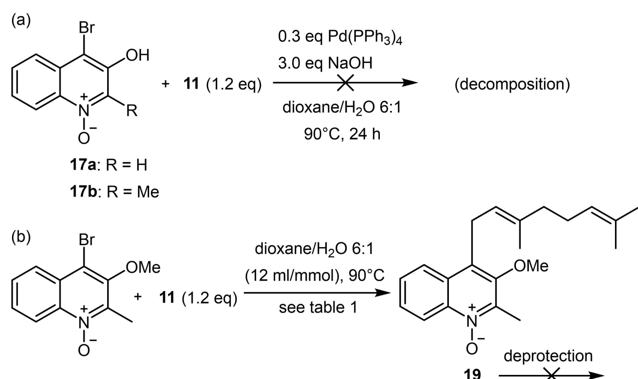


Scheme 4. First experiments for Suzuki-Miyaura coupling of quinolines and geranyl boronic acid (note: boronic esters of **11** like pinacolato gave similar results).

Starting experiments clearly revealed that coupling with non-protected 3-hydroxyquinoline-*N*-oxides **17 a/b** were not successful (Scheme 5a). Different phenol protective groups were tested for introduction (before or after *N*-oxidation), successful Suzuki-Miyaura coupling and finally selective deprotection. During these investigations, Suzuki-Miyaura conditions were further screened and optimized (Scheme 5b). Some results for the readily available methyl protected starting material **18** are depicted in Table 1. Unfortunately, the methyl protective group could not be selectively removed.

With the *p*-methoxybenzyl protective group, however, we could realize a prosperous sequence **20**→**24** involving introduction, Suzuki-Miyaura coupling and



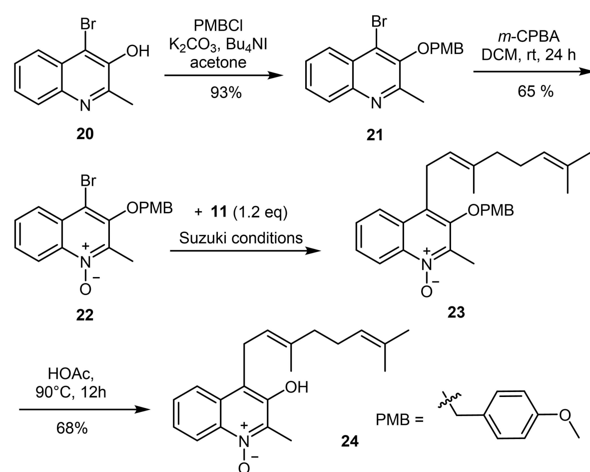
Scheme 5. Suzuki-Miyaura coupling of 4-bromo-3-hydroxyquinoline-*N*-oxides and boronic acid **11**.

acid cleavage (Scheme 6).[21] Compound **24** can be called as the geranyl analogue of Aurachin B (**3**).

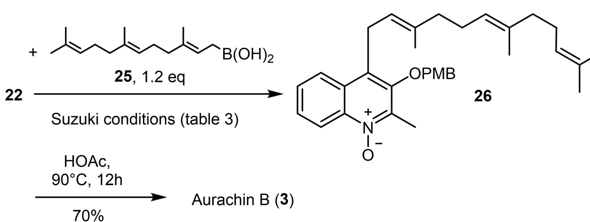
For the Suzuki-Miyaura coupling (**22**+**11**) using the formerly optimized conditions (table 1) we realized no decrease of yield caused by the sterically more demanding PMB protective group (table 2, entry 1). Nevertheless, we initiated further approvement of different reaction conditions. Best results were obtained using 0.1 eq. $Pd(OAc)_2$/dppb (entry 3). The yields moderately dropped when decreasing the catalyst rate (entries 4/5).

Now our best condition found during the synthesis of "geranyl Aurachin B" (**24**) were used to obtain Aurachin B (**3**) itself replacing the geranyl boronic acid (**11**) by the farnesyl analogue **25** (Scheme 7). The yields dropped down, mainly with respect to solubility effects (Table 3, entries 1/2). Slight modification again resulted in acceptable yield (entry 3). The spectroscopical data for **3** significantly matched those reported in the literature (see Supp. Inf.).[1]

The biogenetic studies towards the synthesis of natural Aurachin A (**4**) suggest a side chain epoxidation of Aurachin B (**3**) followed by spontaneous *trans*-selective ring-opening (Scheme 1). Whereas bacterial monooxygenases are competent for regioselective epoxidation, standard chemical methods are not for similar electron rich double bonds. Not surprisingly, Prilezhaev type epoxidation of **3** or **24** resulted in



Scheme 6. Synthesis of geranyl Aurachin B (**24**).



Scheme 7. Synthesis of Aurachin B (**3**).

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Table 1. Suzuki-Miyaura coupling of 4-bromo-3-methoxy-2-methylquinoline-*N*-oxide **18** and boronic acid **11**.[a]

Entry	Pd source	Ligand	Base	Time	Yield
1	0.3 eq. $Pd(OAc)_2$	0.4 eq. dppf[b]	2.0 eq. Cs_2CO_3 or K_2CO_3	72 h	30%
2	0.3 eq. $Pd(dppf)Cl_2$	–	4.0 eq. K_2CO_3	72 h	62%
3	0.3 eq. $Pd(OAc)_2$	0.4 eq. dppb[c]	2.0 eq. Cs_2CO_3	72 h	41%
4	0.3 eq. $Pd_2(dba)_3$[d]	0.6 eq. SPhos[e]	2.0 eq. Cs_2CO_3	72 h	46%
5	0.05 eq. $Pd_2(dba)_3$	0.075 eq. *rac*-BINAP	2.0 eq. Cs_2CO_3	48 h	71%
6	0.3 eq. $Pd(dba)_2$	0.3 eq. SPhos	2.0 eq. Cs_2CO_3	72 h	60%
7	0.05 eq. $Pd(PPh_3)_4$	–	2.0 eq. Cs_2CO_3	72 h	54%

[a] In general 1.2 eq. **11**, dioxane/H_2O 6:1 12 mL/mmol, 90 °C; decomposition at > 100 °C; CsF was also tested as a base, but it gave poor results.
[b] dppf = 1,1‘-bis(diphenylphosphino)ferrocene.
[c] dppb = 1,4-bis(diphenyl-phosphino)butane.
[d] dba = dibenzylideneacetone.
[e] SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Table 2. Suzuki-Miyaura coupling of quinoline-*N*-oxide **22** and boronic acid **11**.[a]

Entry	Pd source	Ligand	Base	Time	Yield
1	0.05 eq. $Pd(PPh_3)_4$	–	2.0 eq. Cs_2CO_3 (or Na_2CO_3)	48–96 h	65–69%[b]
2	0.05 eq. $Pd(OAc)_2$	0.075 eq. dppf	2.0 eq. Cs_2CO_3	72 h	77%
3	0.1 eq. $Pd(OAc)_2$	0.1 eq. dppb	2.0 eq. Cs_2CO_3[c]	24–48 h	80–90%
4	0.05 eq. $Pd(OAc)_2$	0.05 eq. dppb	2.0 eq. Cs_2CO_3	24–48 h	64%
5	0.02 eq. $Pd(OAc)_2$	0.02 eq. dppb	2.0 eq. Cs_2CO_3	24–48 h	67%

[a] 1.2 eq. **11**, dioxane/H_2O 6:1, 12 ml/mmol, 90 °C; solvent screening: similar results for toluene/H_2O 7:3; further tested: dioxane, H_2O, DMF, DMF/H_2O, toluene.
[b] Compare Table 1, entry 7.
[c] Yield significantly decreased with NaOAc or DMAP.

Table 3. Suzuki-Miyaura coupling of quinoline-*N*-oxide **22** and boronic acid **25** (1.2 eq.).[a]

Entry	Pd source	Ligand	Solvent	Yield
1	0.05 eq. $Pd(PPh_3)_4$	–	dioxane/H_2O 6:1	33%
2	0.1 eq. $Pd(OAc)_2$	0.1 eq. dppb	dioxane/H_2O 6:1	34%
3	0.1 eq. $Pd(OAc)_2$	0.1 eq. dppb	toluene or toluene/H_2O 7:3	65%

[a] Other conditions: 2.0 eq. Cs_2CO_3, 90 °C, 48 h.

product mixtures. Looking at the *ortho*-hydroxyl group in **24**/**3** we speculated that Sharpless-Katsuki conditions[22] could allow regioselective epoxidation with directing effect of the hydroxyl group which, of course, is not in the original allylic position.[23] Different Sharpless-Katsuki protocols were tested and failed, presumably caused by solubility and workup problem.[22–24] We were delighted that slightly modified Sharpless-Katsuki conditions with basic workup involving aqueous NaF[25] resulted in a one pot epoxidation-ring opening five-membered cyclization sequence **24**→**27a**→**28** with geranyl Aurachin **24** as testing molecule (Scheme 8). Similar results (28–42% yield) with optimized epoxidation conditions (−10 °C for 15 h) were obtained for the transformation Aurachin B (**3**)→Aurachin A (**4**). Again, the spectroscopical data for **4** significantly matched those reported in the literature (see Supp. Inf.).[1,14]

Although we used the common and readily available *L*-(+)-diethyl tartrate we did not expect any effect of enantioselectivity.[23] Nevertheless, an HPLC analysis on chiral phase with CD-detection revealed enantiomeric excess of 10–24% ee in different experiments. For verification, *D*-(−)-tartrate was tried resulting in similar ee for the opposite enantiomer whereas *meso*-diethyl tartrate yielded a 50:50 mixture in all cases (see Supp. Inf.). This effect is a clear evidence for the

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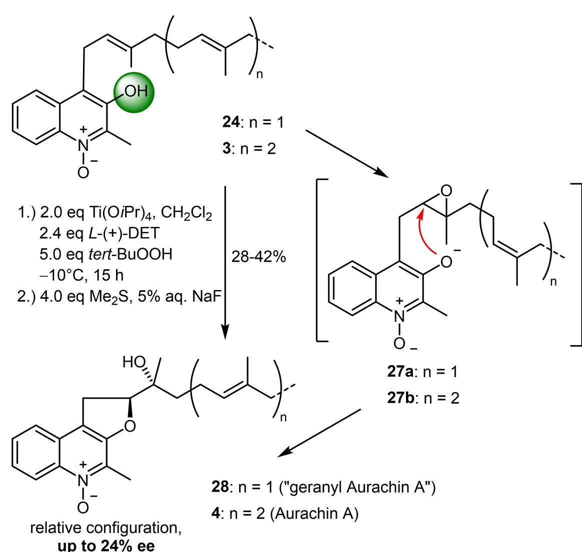

Scheme 8. Side chain epoxidation followed by spontaneous trans-selective ring-opening.

phenolic hydroxyl group being involved with the epoxidation step.

Conclusion

Our cross-coupling approach for the syntheses of Aurachins from appropriate haloquinoline derivatives and polyprenyl boronic acids resulted in an extensive study of this up no now unknown substrate combination. We found that haloquinoline-*N*-oxides can be reacted with geranyl or farnesyl boronic acid. This tool could be utilized for the synthesis of the natural product Aurachin B from the myxobacterium *Stigmatella aurantiaca.* This prenylated quinoline could then be transformed into the related Aurachin A through an epoxidation-ring opening cascade.

Experimental Section

Experimental Details

General Procedure: Suzuki-Miyaura Coupling using Pd Source and Ligands

In a flame-dried Schlenk flask/tube under argon atmosphere 1,4-dioxane/H_2O (6:1 v/v, 12 mL/mmol) was degassed with argon for 15 min. The Pd source as well as the ligand (equivalents see tables) were added and heated to 50 °C for 30 min. After cooling to room temperature, the particular base (equivalents see tables) followed by the haloquinoline (1.0 eq.) and followed by the boronic acid (in general 1.2 eq.) were added. The mixture was heated to 90 °C for 24–96 h (see tables).

After cooling to room temp, H_2O (100 mL/mmol) was added and the mixture was extracted with EtOAc (3 × 100 mL/mmol). The combined organic layers were washed with brine (100 mL/mmol), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography (*n*-hexane or petroleum ether/EtOAc).

General Procedure 5: Modified Sharpless-Katsuki Side Chain Epoxidation

To Ti(O*i*Pr)$_4$ (0.06 mL, 0.20 mmol, 2.0 eq.) in anhydrous CH_2Cl_2 (1.00 mL) under argon atmosphere at −10 °C was added diethyl tartrate [*L*(+)-DET or *D*(−)-DET or *meso*-DET) (0.04 mL, 0.24 mmol, 2.4 eq.) with additional stirring for 5 min. The particular 4-„prenyl"-3-hydroxy-2-methylquinoline-1-oxide (0.10 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (0.5 mL) followed by *tert*-BuOOH (5.5 M in decane, 0.09 mL, 0.5 mmol, 5.0 eq.) were added at −10 °C and the mixture was stirred for additional 15 h at −10 °C. (Note: The yield optimum of 28–42% was observed in the range 0° to −10 °C for reaction temperature; more impurities at > 0 °C, low yield at more decreased temperature).

Dimethyl sulfide (0.03 mL, 0.40 mmol, 4.0 eq.) was added with additional stirring for 40 min. The mixture was then poured into a NaF solution (5%, 3.0 mL, double volume of CH_2Cl_2) with stirring for 20 h at room temperature. The mixture was saturated with NaCl (solid) and filtered through Celite® rinsing with H_2O (50 mL), CH_2Cl_2 (50 mL) und EtOAc (50 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography.

Supplementary data (experimental procedures, NMR, HR MS, HPLC, HPLC-CD…) associated with this article can be found, in the online version, at https://doi.org/.

Acknowledgements

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