General Synthetic Approach to Rotenoids via Stereospecific, Group-Selective 1,2-Rearrangement and Dual S_NAr Cyclizations of Aryl Fluorides

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Dedicated to the memory of the late Professor Sho Ito

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1 Introduction

We wish to report a general synthetic route to rotenoids, a class of plant-derived natural products of traditional importance as well as of recent interest by newly-found biological activities. Our full account is structured as follows, (1) introduction, including historic interest, biosynthesis, and previous syntheses, and (2) syntheses of several rotenoids via our present strategy.

1.1 Historic Interest in Rotenoids

In tropical regions in East Asia and South America, various leguminous plant species, including Derris and Lonchocarpus, have traditionally been used as insecticides and fish poison. The latter is associated with ‘lazy fishing’, that is, dusting the powdered root on the water surface and collecting the floating fish, which can be eaten.

Research on the toxic ingredients led to the isolation of a series of compounds, termed as the rotenoids (Figure 1). The major component, rotenone (1), was isolated as early as 1896,2 and its structure was elucidated in 1932 by three independent groups led by Takei,3a Butenandt,3b and LaForge.3c The absolute stereochemistry of 1 was determined by Büchi in 1961.4 Other minor congeners, deguelin (2) and tephrosin (3), were isolated in 1931 by Clark,5a,b In 1932, the structures of 2 and 3 were assigned by Clark5c and by Butenandt,5d respectively. It is interesting to note that the name, rotenone, originated from the Taiwanese name of the plant (Figure 2) in combination with the ketone functionality, that is, 'roten' (Fish wisteria) + 'one'.

Figure 1 Natural rotenoids

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Abstract A general synthetic approach to rotenoids is described, featuring 1) stereospecific, group-selective 1,2-rearrangements of epoxy alcohols, and 2) S_NAr oxy-cyclizations of aryl fluorides. The common intermediate epoxyketone, en route to (–)-rotenone and (–)-deguelin, was prepared from D-araboascorbic acid in five steps. Also described is the conversion of (–)-deguelin into oxidized congeners, (–)-tephrosin and (+)-12a-epi-tephrosin.

Key words isoflavonoid, rotenoid, semi-pinacol rearrangement, S_NAr cyclization, total synthesis

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Their toxicity originates from the interference of the ubiquinone oxidoreductase of the respiratory electron transport chain.\textsuperscript{1} Upon ingestion, the compounds are relatively innocuous to mammals, being rapidly metabolized, while fish and insects lack such a detoxification mechanism. Frightening enough, however, a recent report stated that 1 and 2 are causative agents of Parkinson disease.\textsuperscript{6} On the other hand, significant reports have appeared on the antitumor effects of 2\textsuperscript{7a} and 3,\textsuperscript{7b} which evoked considerable attention of biological research and also chemical synthesis.

Biographical Sketches

**Seiya Matsuoka** was born in 1994 in Kanagawa, Japan. He received his B.Sc. degree (2017) from Tokyo Institute of Technology under the supervision of Prof. Keisuke Suzuki. He is currently a master course student.

**Kayo Nakamura** was born in 1987 in Kagoshima, Japan. She received her B.Sc. (2010), M.Sc. (2012), and D.Sc. (2016) from Tokyo Institute of Technology under the supervision of Prof. Keisuke Suzuki and Prof. Ken Ohmori. After working as a postdoctoral fellow at Tokyo Institute of Technology with Prof. Keisuke Suzuki and Prof. Ken Ohmori (2016.4–2016.8) and at the University of Hawaii with Prof. Marcus A. Tius (2016.9–2017.12), she worked at Gly-Tech, Inc. as a contract employee (2018.1–2018.3). She is currently working in Riken as a postdoctoral fellow with Dr. Katsunori Tanaka.

**Ken Ohmori** received B.S. (1991), M.S. (1993), and Ph.D. (1996) degrees from Keio University under the direction of Professor Shosuke Yamamura. In 1996, he became an Assistant Professor at the Department of Chemistry, Tokyo Institute of Technology, joined Prof. Keisuke Suzuki’s group, and was promoted to Associate Professor at the university (2007).

**Keisuke Suzuki** received his D.Sc. in 1983 from the University of Tokyo (Prof. Teruki Mukaiyama), and became a Research Associate (the late Prof. Gen-ichi Tsuchihashi) at Keio University (1983), where he was promoted to Lecturer (1987), Associate Professor (1989), and Professor (1994). He moved to his current position at the Department of Chemistry, Tokyo Institute of Technology (1996–). He spent his sabbatical as a visiting Professor at ETH, Zürich (1990.3–1991.3; Prof. D. Seebach) and Regensburg (2010.6–2010.8; Prof. O. Reiser).
1.2 Biosynthesis

As a subclass of the isoflavonoid natural products, the biosynthesis of rotenoids starts with the assembly of the polyketide–shikimate scaffold A (Scheme 1). Claisen condensation and oxy-Michael reaction give flavanone B, which undergoes P-450-initiated generation of a radical species, inducing 1,2-shift of an aryl group to form isoflavone C, and dehydration to give isoflavone D. After installation of additional oxygen functions on the A ring and methylation to give E, oxidative transformation of the O-methyl group triggers a cyclization to form the B-ring as in H. Installation of an isoprenyl group forms rotenoic acid (I), which is a branching point to rotenone (1) via a 5-exo-cyclization and deguelin (2) via a 6-endo-cyclization.

1.3 Synthetic Studies

Synthetic studies of rotenoids started in the mid-20th century, and early successes include the total syntheses of (±)-1 (Matsui, 1960), (±)-2 [(Fukami, 1960) and (Yamashita, 1974)], and (−)-1 (Yamashita, 1979). After a hiatus, synthetic interest has recently resurged by the discovery of novel bioactivities in minor rotenoids, including 2 and 3. Since rotenone (1) is readily available from natural sources, several semi-syntheses of 2 from 1 have been devised. However, total synthesis reports have appeared as well, including (±)-2 [(Sames, 2003) and (Xu, 2018)], and (−)-2 [(Winssinger, 2010), (Scheidt, 2013), and (Suh, 2015)]. Approaches to tephrosin (−)-3 (Winssinger, 2010) and of (±)-3 (Xu, 2018) have appeared as well.

In connection with our synthetic studies on the flavonoid- and isoflavonoid-class of polyphenols, we became interested in the synthesis of the rotenoids. In due course, we reported the total syntheses of (−)-1 and (−)-dalpanol (4) in 2016 as a rapid communication. The purpose of this paper is to outline our general synthetic approach, featuring the use of the group-selective, stereospecific 1,2-rearrangements of epoxy alcohol J followed by folding the product K into the tetracyclic scaffold L by dual $S_{N}$Ar oxy-cyclizations of an aryl fluoride by an internal alkoxide (Scheme 2).
Before going into the detail, it would be appropriate to give a small overview of the semi-pinacol-type 1,2-shifts, centering attention to the group selectivity and the stereochemical integrity.

### 1.4 General Issues of 1,2-Rearrangements

Concerning the semi-pinacol rearrangement of compounds with the general formula M, let us focus on the following two aspects (Figure 3).

The group selectivity refers to the selectivity, among the two potential migrating groups, A and B, which undergoes the 1,2-shift. Two factors are relevant, namely a) migratory aptitudes of A and B, and b) effect of the stereochemistry of the reactant M.

In addition, the reaction may proceed either with inversion of the pre-existing stereogenic center (stereospecific) or with racemization, depending on the nature of the reaction, reflecting the concerted or stepwise nature of the bond reorganization events, namely departure of the leaving group, and the 1,2-shift.

#### 1.4.1 Curtin–Collins Experiments

Around 1950, Curtin published the pioneering work on the effect of the stereochemical (conformation/configuration) of reactants on the reactivity (Scheme 3). Deamination of semi-pinacol rearrangement was the subject that led him to a concept, later called as the Curtin–Hammett principle. Diastereomeric amino alcohols la and lb, upon diazotization, gave markedly different product distributions. While la mostly gave II by the anisyl shift, and a minor amount of III was formed by the phenyl shift. The tendency was opposite for the diastereomer lb, giving the phenyl-shifted product III as the major product. The latter example is striking in view of the high migratory aptitude of an anisyl group, 10^3 times higher than that of a phenyl group in pinacol rearrangement, which clearly shows the importance of the stereochemical selectivity of the reactants.

In 1957, Collins provided insight into the conformational factor using ingeniously designed tracer experiments (Scheme 4). The semi-pinacol rearrangement of chiral, non-racemic (S)-IV gave mostly V (inversion), but with partial racemization (76% ee). The same experiment, but using stereospecifically labeled IV' (Ph* designates a 14C-labeled phenyl group), showed that the inversion product, (S)-V', is produced by the Ph* shift, while the retention product, (R')-V, is derived from the Ph shift. The implication is that the reaction proceeds via an open carbenium ion, which does not last long enough for the free bond rotation around the C–C bond. Reflecting the most stable conformers of the parent diazonium ion VI, the initially-formed carbenium ion is VIIa, which undergoes the 1,2-shift of Ph* (inversion), while a competing C–C bond rotation of VIIa allows a partial leakage to the second carbenium ion conformer VIIb, which undergoes 1,2-shift of the Ph group (formally retention).

Overall, due to the super-leaving ability of N2 from aliphatic diazonium salts, the reaction takes on a typical SN2 process, which was indeed achieved as follows.

#### 1.4.2 Pinacol-Type Rearrangements of α-Mesyloxy Alcohols Promoted by Organooaluminum Reagents

In 1983, we reported that chiral, non-racemic methanesulfonyloxy alcohol VIII, upon treatment with Et3Al as a Lewis acid, undergoes stereospecific 1,2-rearrangement with inversion of the pre-existing stereogenic center (Equation 1). Importantly, even when the starting material is a diastereomeric mixture at the tert-alcohol center, the 1,2-shift takes place in a group-selective manner, if the po-
tential migrating groups differ significantly in their migrat-
tory aptitudes. The Lewis acid activation through a seven-
membered chelate $A$ allows a smooth reaction to proceed.
Flexibility of the seven-membered chelate explains the se-
lective migration of the group of higher migratory aptitude
by placing itself at the antiperiplanar position to the leaving
group.

On the other hand, Equation 2 exemplifies a reaction
where the tert-alcohol stereogenic center is decisive for the
group selectivity.\(^{20}\) Note that the potential migrating
groups, ethyl and octyl, are of essentially the same migra-
tory aptitudes. Under carefully defined conditions to gener-
ate an aluminum alkoxide, a high group selectivity is ob-
served as accounted by the chelation model. The 1,2-shift of
alkyl groups is also stereospecific.

In 1986, we published a joint paper\(^{21a}\) with the
Yamamoto–Maruoka group at Nagoya, reporting Lewis acid
promoted rearrangements of epoxy alcohols and the corre-
sponding silyl ethers into aldol products.\(^{21a}\) Later, we ex-
ploried the synthetic utility of the 1,2-shift-based aldol syn-
thesis in various natural product syntheses.\(^{21b,c,22}\) Scheme 5
illustates a divergent sytheses of antifungal natural pro-
ducts, averaciolide and isoaveraciolide, featuring several im-
portant aspects of synthetic utilities.\(^{21b,c}\) First, the 1,2-shift
proceeds stereospecifically, allowing clean conversions of
trans-epoxy alcohols, XII and XV, into anti-aldols, XIII and
XVI. Although not shown, vice versa is true in converting
cis-epoxy alcohols into syn-aldol compounds. Second, al-
though the starting materials XII and XV are diastereomeric
mixtures, exclusive migration of the vinyl groups occur,
which could be ascribed to the relative migratory aptitudes
(vinyl >> alkyl). Conformational flexibility allows both dis-
tereomers to adopt the respective ‘reactive conformers’
placing the vinyl group antiperiplanar to the epoxide C–O
bond to be cleaved upon Lewis acid activation, manifesting
a typical Curtin–Hammett system.\(^{16}\) Third, note that an $\alpha$
-silylvinyl group has an excellent migratory aptitude, which
was previously discovered in the pinacol-type rearrange-
ment.\(^{23}\) Also interestingly, depending on the presence or
the absence of TMS group, the stereochemical course of the
reduction of aldol products is different, as explained by the
hydrogen-bonded models $A$ and $B$, respectively.\(^{21c}\) These
features were exploited in the present project as will be dis-
cussed later.

1.4.3 Epoxy Alcohol $\rightarrow$ Aldol Rearrangements

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2 Results and Discussion
2.1 Synthetic Planning – A Thought Process

In the following, the thought process how our synthetic
plan evolved will be described. The starting point was our
recent study on the flavonoid- and isoflavonoid-class natu-
ral products, through which two powerful tactics relevant
to the rotenoid synthesis have been developed.
Tactic #1 was the S$_{Ar}$ oxy-cyclization of aryl fluorides, working even without resorting to electron-withdrawing group(s), such as a nitro group (Equation 3).24b

Tactic #2 was an approach to isoflavonoids based on the 1,2-shift of flavonoids inspired by the biosynthesis (Equation 4).25 Activation of catechin-derived mesylate XX with an organoaluminum reagent effects 1,2-shift of an aryl group, and the intermediary oxonium species is captured by an aluminum ligand, giving XXI. The process is characterized by a thorough stereospecificity (perfect enantiomeric excess) and a perfect trans-selectivity.

For the rotenoid synthesis, however, application of tactic #2 was unrealistic for two reasons, (1) the 2,3-cis stereochemistry was required, and (2) finding a ‘–CH$_2$OH’ equivalent was not straightforward (Scheme 6A).

Aa an alternative, we came up with an idea of a similar 1,2-shift, but placing the migrating aryl group at the C-4 position rather than at the C-2 position (Scheme 6B). Still there was a problem, in that stereoselective preparation of the starting material C seemed uneasy.

As a potential countermeasure, we centered our attention to the epoxy alcohol → aldol rearrangement.21 If one started with cis-epoxy alcohol E, stereospecific 1,2-shift of an aryl group would give syn-aldol F (Scheme 6C). We selected two aryl groups possessing an o-fluoro group, expecting their utilities for the construction of the B and C rings by means of S$_{Ar}$ reactioons. A key question was the group selectivity in the 1,2-rearrangement. While the competing shift of the D-ring (red) gives the isomeric product (not shown), the desired product F is obtained by the 1,2-shift of the A-ring (blue). Given the latter case, the aldol F has a functional pattern ideally suited for constructing two tetrahydropyran rings by dual S$_{Ar}$ oxy-cyclizations.

As discussed above, such group selectivity could be influenced by the relative migratory aptitude and/or the conformational effect. In the present case, both aryl groups share a similar substitution pattern possessing an o-fluoro group, and thus, their intrinsic migratory aptitudes appeared to be similar. Therefore, our initial study was centered at examining the group selectivity of the 1,2-rearrangement by using a substrate within the context of the rotenone synthesis.14

### 2.2 Preliminary Study on 1,2-Rearrangement

Scheme 7 shows the preparation of the substrate 9 for the 1,2-shift, in which we arbitrarily installed the DE-ring first followed by the A-ring.14 Fluorobenzene 6 was lithiated (s-Buli, Et$_2$O, TMEDA, –78 °C, 1 h) and combined with chiral, non-racemic epoxy amide 5, giving epoxypetone 7 in 72% yield. Bromide 8 was subjected to bromine–lithium exchange (n-Buli, Et$_2$O, –78 °C, 1 h) and combined with ketone 7, where stereoselective reaction occurred to give epoxy alcohol 9 as a single product. The stereochemical course of the addition could be explained by chelation model A. Notably, an excellent stereoselectivity was observed, which could be due to the presence of the cis-substituent that effectively blocks the nucleophilic attack from the right side.23
Scheme 8 shows the key 1,2-rearrangement of epoxy alcohol 9. Upon treatment with BF₃·OEt₂ (CH₂Cl₂, 0 °C), epoxy alcohol 9 smoothly reacted within 20 minutes. Assuming the potential lability of the aldol products (e.g., undergoing dehydration, retro-aldol reaction and/or epimerization), the crude products were treated with NaBH₄ in methanol. Diol 11 was obtained as the single product, derived from the 1,2-shift of the DE-ring unit (red). Unfortunately, the wrong group underwent migration regarding the anticipated total synthesis of 1. Importantly, however, we were able to understand the stereochemical course of the reactions by careful 1H NMR analysis, after conversion of diol 11 into anisylidene acetal 12. Two conclusions were: (1) the 1,2-shift occurred stereospecifically with an inversion, and (2) the reduction of the aldol product 10 was stereoselective, as rationalized by model B.

Even though the undesired isomer was obtained, the perfect group selectivity gave us valuable insight. Scheme 9 shows two hydrogen-bonded conformers of epoxy alcohol 9, where conformer 9b is disfavored by steric hindrance caused by the cis-substituent R (CH₃OTBS). Conformer 9a would be highly populated, a hypothesis, which was supported by calculations on a simple model substrate (R = Me, and aryl = Ph), showing an energy difference as large as 5.4 kcal/mol.

Assuming 9a to be essentially the sole conformer present, the D-ring (red) undergoes 1,2-migration, since it is antiperiplanar to the C–O bond (green) that is cleaved upon Lewis acid activation. Note that this interpretation does not contradict the Curtin–Hammett principle, and just corresponds to one of the prototypical categories, where both conformers react at a similar rate (i.e., similar migratory aptitudes), and the conformer ratio (virtually exclusively 9a) is reflected in the product distribution.

This result gave us a clear and simple guideline to achieve the group-selective 1,2-rearrangement (Scheme 10): An ‘empirical rule’ is ‘Install the migrating group first!’. The hope was simply that, by reversing the order of installing two aryl groups (i.e., first the A-ring to give I followed by the D-ring), the diastereomeric substrate III would be produced, which in turn would undergo 1,2-shift of the A-ring in a group-selective manner.

To our delight, this scenario has been successfully realized, allowing a unified synthetic route to the total syntheses of (−)-rotenone (1) and (−)-deguelin (2). Although the...
synthesis of 1 has been reported as a communication,\textsuperscript{14} sizable improvements have been made thereafter, which will be described in the following.

### 2.3 Synthesis of (–)-Rotenone (1)

Total synthesis of (–)-rotenone (1) was executed as follows: In comparison with our previous report,\textsuperscript{14} one of the improvements is the use of epoxy lactone 16 as a chiral, non-racemic starting material, easily prepared in three steps from d-araboascorbic acid (13), an abundant feedstock (Scheme 11). Oxidation of 13 with H\textsubscript{2}O\textsubscript{2} following an Organic Synthesis procedure\textsuperscript{22} (Na\textsubscript{2}CO\textsubscript{3}, H\textsubscript{2}O, 40 °C, 30 min) with a modified workup gave diol 14 in 94% yield. Regioselective tosylation of 14 (TsCl, pyridine, 0 °C, 14 h) gave tosylate 15 in 76% yield.\textsuperscript{20} Treatment of tosylate 15 with K\textsubscript{2}CO\textsubscript{3} (MeCN, rt, 22 h) gave epoxy lactone 16 in 75% yield via the epimerization at C-2 followed by oxirane formation.\textsuperscript{20}

Bromobenzene 8 was treated with n-BuLi (Et\textsubscript{2}O, –78 °C, 1 h) to effect a halogen–metal exchange, and the resulting lithio species was combined with lactone 16 to give adduct 17, which was in an equilibrium with hemiacetal 18. The 17/18 mixture was treated with tert-butylimidethylsilyl chloride (TBSCl) and imidazole, giving siloxy ketone 19 in 94% yield (2 steps).

Ketone 19 is a common synthetic intermediate of our previous synthesis of 1\textsuperscript{14} as well as the synthesis of deguelin (2) as will be described later. The availability of ketone 19 was significantly improved in a total yield of 50% over five steps, starting from 13. The previous approach used amide 5 as the chiral, non-racemic building block, which was only available in 15% yield in nine steps from diethyl L-tartarate.\textsuperscript{14}

Next, the DE-ring unit 6 was lithiated (s-BuLi, Et\textsubscript{2}O, TMEDA, –78 °C, 1 h), and allowed to react with ketone 19 to give epoxy alcohol 20 in 89% yield (Scheme 12). As expected, epoxy alcohol 20 was obtained as a single diastereomer, which proved to be epimeric to 9.\textsuperscript{14} Pleasingly, the reaction of epoxy alcohol 20 with BF\textsubscript{3}·OEt\textsubscript{2} (20 mol%, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 15 min), followed by the reaction with NaBH\textsubscript{4} cleanly gave diol 21 as a single isomer in 71% yield. It should be noted that 21 was the product that is derived from the migration of the A-ring (blue) (cf. diol 11) as ascertained by extensive NMR study.\textsuperscript{14} The stereochemical course of the two-step reaction 20→21 (1,2-shift followed by reduction) proved perfect by the careful analysis after conversion into anisylidene acetal 22, which also served as an advance intermediate en route to (–)-rotenone (1).

Acetal 22 was converted into the pentacyclic rotenoid skeleton via two S\textsubscript{N}Ar oxy-cyclizations (Scheme 13). Upon treatment of 22 with n-Bu\textsubscript{4}NF (THF, rt, 1 h), the TBS group was removed, giving alcohol 23 in 98% yield, ready for the S\textsubscript{N}Ar oxy-cyclization. After screening of the conditions, the projected reaction was achieved by using t-BuOK in the presence of catalytic amounts of Ni(cod)\textsubscript{2} (10 mol%) and PCy\textsubscript{3} (30 mol%) (toluene, reflux, 2 h), giving tetrahydropropyran 24 in 86% yield. Upon treatment with AlH\textsubscript{3}\textsubscript{31} anisylidene acetal 24 was regioselectively cleaved, giving alcohol 25 as a single isomer (79% yield). The S\textsubscript{N}Ar oxy-cyclization of 25 proceeded smoothly (NaH, 15-crown-5, toluene,
Finally, treatment of 4 with Burgess reagent\textsuperscript{33} A gave 1 in 50% yield. A side product, benzofuran 29, was obtained in 13% yield, arising most likely from the tertiary cation generation followed by a 1,2-hydride shift. Recrystallization from benzene gave 1 as colorless crystals (mp 153–154 °C, [α]_D\textsuperscript{23} −1.5 × 10^2 (c 0.52, CHCl_3) [Lit.\textsuperscript{11} mp 165–166 °C, [α]_D\textsuperscript{23} −177 (c 2, CHCl_3)]. All the physical data of the synthetic sample of 1 coincided with the reported data.\textsuperscript{11,34} Direct comparison was done with an authentic sample ([H and \textsuperscript{13}C NMR, IR, HRMS]).\textsuperscript{35}  

### 2.4 Total Synthesis of (−)-Deguelin (2)  

Since deguelin (2) is one of the rotenoids that is attracting recent interest by its anticancer activity,\textsuperscript{7a} we decided to apply the above-stated synthetic route to the synthesis of 2, as described in this section.

Scheme 14 shows the preparation of the DE-ring unit 34 for the synthesis. 3-Fluorophenol (30) was protected as a THF ether to give fluorobenzene 31 (88% yield).\textsuperscript{36} Regioselective lithiation of 31 (n-BuLi, HMPA, THF, −78 °C, 1 h) and treatment with prenyl bromide (THF, −78 °C, 1 h) gave the prenylated product 32, which was hydrolyzed (cat. PPTS, EtOH, 60 °C, 6 h) to give phenol 33 in 92% yield (2 steps). Oxidative cyclization of phenol 33 using PdCl\textsubscript{2} and CuCl\textsubscript{2} under air\textsuperscript{37} gave the DE-ring unit 34 in 74% yield.

Scheme 15 illustrates the synthesis of epoxy alcohol 35 for the projected 1,2-shift. ortho-Lithiation of 34 with s-BuLi (Et,O, TMEDA, −78 °C, 1 h) followed by reaction with ketone 19 gave epoxy alcohol 35 in 85% yield as a single diastereomer. The stereostructure of 35 was assigned as shown based on \textsuperscript{1}H NMR and NOE analyses. The projected 1,2-rearrangement of epoxy alcohol 35 was achieved by treatment with BF\textsubscript{3}·OEt\textsubscript{2} (20 mol%, CH\textsubscript{2}Cl\textsubscript{2}, −15 °C, 40 min). The crude material containing aldol 36 was immediately reduced with i-Bu\textsubscript{3}AlH, giving diol 37 as a single diastereomer in 88% yield (2 steps). HMBC-analysis shown below verified that diol 37 was derived from the 1,2-shift of the A-ring. The stereochemical relations of C-2, C-3, and C-4 stereogenic centers were concluded at the stage of anisylidene acetal 38, which was obtained by acetalization of 1,3-diol 37 followed by removal of the TBS group in 89% yield (2 steps). The stereochemistry was identified as such by NOE analyses, verifying that (1) the stereospecificity of the 1,2-shift (inversion), and (2) the facial selectivity of the i-Bu\textsubscript{3}AlH reduction.
Having acetal 38 as an advanced intermediate, the next stages were the formations of the B- and C-pyran rings by dual S$_2$Ar oxy-cyclizations (Scheme 16). The S$_2$Ar reaction of 38 proceeded smoothly by the action of i-BuOK (3.0 equiv, toluene, reflux, 1.5 h), giving ether 39 in 74% yield. It is notable that use of the Ni catalyst was necessary in the corresponding rotenone synthesis (see 23 → 24, Scheme 13). By contrast, the permit case, 38 → 39, did not need the Ni catalyst. Treatment of ether 39 with i-Bu$_2$AlH allowed regioselective C−O bond cleavage to give alcohol 40 in 93% yield. The regioselectivity can be explained by Al-coordination to the C-2 oxygen with less steric hindrance. Note that AlH$_3$ was used for this purpose in the synthesis of 1 (see 24 → 25, Scheme 13). i-Bu$_2$AlH turned out to be superior for this transformation. The second S$_2$Ar oxy-cyclization of alcohol 40 proceeded smoothly using NaH [2.0 equiv, 15-crown-5 (1.0 equiv), toluene, DMPU (9:1), 80 °C, 2 h], giving ether 41 in 95% yield.

Finally, ether 41 was converted into the natural product, (−)-deguelin (2). Removal of the MPM group in 41 with DDQ$^{39}$ [2,6-di-tert-butylpyridine, 1,4-dioxane, H$_2$O (8:1), 50 °C, 1 h] gave alcohol 42 in 72% yield. We noted that small amounts of diol 43 was formed (11% yield) due to the oxidation at the benzylic position, which was convertible into (−)-tephrosin (3) – an oxidized rotenoid congener (vide infra). Oxidation of alcohol 42 with IBX (DMSO, rt, 6.5 h) gave (−)-deguelin (2) as a yellow amorphous solid in 82% yield. All the physical data ($^1$H, $^{13}$C NMR, IR, high-resolution MS) of the synthetic material 2 coincided with those of the reported data: $\alpha$$_{D}^{20}$ –46 (c 0.20, CHCl$_3$) {Lit.$^{40c}$ $\alpha$$_{D}^{20}$ –45 (c 0.2, CHCl$_3$)}.

2.5 Total Synthesis of (−)-Tephrosin (3)

As noted in the introduction, novel biological activities$^{1b}$ in rotenoids have evoked considerable attention to this class of compounds, including (−)-tephrosin (3).

As described earlier (Scheme 16), we noted that diol 43, a side product of the oxidative deprotection of 41, could be regarded as an immediate precursor of 3. Indeed, oxidation of 43 (IBX, DMSO, rt, 5.5 h) gave 3 as a white amorphous solid in 82% yield (Scheme 17). All the physical data ($^1$H, $^{13}$C NMR, IR, high-resolution MS) of the synthetic material 3 matched with the reported data: $\alpha$$_{D}^{20}$ –98 (c 0.20, CHCl$_3$) {Lit.$^{40c}$ $\alpha$$_{D}^{20}$ –86 (c 0.2, CHCl$_3$)}.
Furthermore, seeking for a more practical route to 3, we examined the oxidation of the synthetic (–)-deguelin (2). Recently, two reports appeared on this conversion: Russell41 used K2Cr2O7 for converting (–)-2, obtained from natural rotenone (–)-1, while Xu10e reported a protocol, which was applied to the racemate of 2. We tested these protocols and other potential oxidants on our synthetic material (–)-2, finding interesting difference in the stereochemistry and the product composition, as described below.

First, the Russell method was applied to (–)-2 [K2Cr2O7, AcOH, H2O (3:1), 60 °C, 0.5 h], which cleanly gave (–)-3 in 94% yield ([α]D20 –84 (c 0.23, CHCl3)] (Table 1, entry 1). The HPLC analysis using chiral stationary phase proved the enantiomeric purity of the product within the limit of the analysis [(a); Figure 4].

In contrast, the result was markedly different with the Xu protocol (Table 1, entry 2). Upon exposure of (–)-2 to O2 (1 atm) in the presence of Cu2O and TBD (DMSO, rt, 4.5 h), a separable mixture of two products formed. After separation by preparative TLC (hexane/EtOAc 1:1), the less polar product (Rf = 0.65) was the desired product 3 (53% yield), while the more polar one (Rf = 0.51) was the epimer 44 (27% yield), which is also a natural product, 12a-epi-tephrosin, derived from the same plant that produces 3. To our surprise, the [α]D values of these compounds were almost zero,43 suggesting almost complete racemization, which proved indeed the case as verified by the HPLC analyses on chiral stationary phase [(b) and (c) in Figure 4]. Equation 5 shows a rationale of the racemization at the C-6a center by base-induced retro-Michael/Michael reaction, proceeding more rapidly than the rate of the C12a hydroxylation.

In addition, IBX worked as an oxidant (DMSO, 60 → 80 °C, 19 h) giving 3 (44%) and 44 (44%) (Table 1, entry 3), respectively. In contrast to the result of the air oxidation stated above, both products 3 and 44 were respectively enantiopure, [(d) and (e) in Figure 4]. This result could be explained by an intramolecular oxygen transfer (Equation 6), albeit with no diastereofacial selectivity.

**Table 1 Conversion of (–)-Deguelin (2) into (–)-Tephrosin (3)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K2Cr2O7, AcOH, 60 °C</td>
<td>3: 94% (&gt;99% ee)</td>
</tr>
<tr>
<td>2</td>
<td>O2, Cu2O, TBD, DMSO, rt</td>
<td>3: 53% (~0% ee), 44: 27% (~0% ee)</td>
</tr>
<tr>
<td>3</td>
<td>IBX, DMSO, 60 → 80 °C</td>
<td>3: 44% (&gt;99% ee), 44: 44% (&gt;99% ee)</td>
</tr>
</tbody>
</table>

**Equation 5 Racemization at the C-12a center**

\[
\text{Racemization at the C-12a center}
\]

**Equation 6 Intramolecular oxygen transfer**

\[
\text{Intramolecular oxygen transfer}
\]
3 Conclusions

In conclusion, a general synthetic route for the rotenoid class of natural products has been developed by exploiting 1,2-rearrangement and $S_{N}Ar$ oxy-cyclizations. The present method realized a facile construction of the benzopyran structure. The viability has been demonstrated by the synthesis of (−)-rotenone and (−)-deguelin and also its conversion into (−)-tephrosin and (+)-12a-epi-tephrosin. The present approach provides a means of comprehensive synthesis of rotenoid-related compounds of biological interest.

All reactions dealing with air- and/or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry argon. Ethereal solvents, CH$_2$Cl$_2$ and toluene were used as received (anhydrous; Kanto Chemical Co., Inc.). DMF, HMPA, TMEDA, and DMPU were distilled prior to use according to standard protocols. For TLC analysis, Merck pre-coated plates (TLC silica gel 60 F$_{254}$, Art 5715, 0.25 mm) was used. Silica gel preparative TLC (PTLC) was performed using plates prepared from Merck silica gel 60 PF$_{254}$ (Art 7747). For flash column chromatography, silica gel 60N (Spherical, neutral, 63–210 μm) from Kanto Chemical was used. Melting point determinations were performed using a Yanaco MP-500 instrument or Mettler Toledo MP70 melting point system, and are uncorrected. 1H, 13C, and 19F NMR spectra were measured on a Jasco P-3000 polarimeter. High-resolution mass spectra were performed using a Yanaco MP-500 instrument or Mettler Toledo MP70 melting point system, and are uncorrected. 1H, 13C, and 19F NMR chemical shifts (δ) are expressed in parts per million (ppm) downfield from internal standard (TMS: δ = 0.00 and hexafluorobenzene: δ = –164.9), and coupling constants are reported in hertz (Hz). Standard abbreviations were used for splitting patterns. IR spectra were obtained using attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra. IR spectra were recorded on a Jasco FTIR-6300. Optical rotations ([α]$_D$) were measured on a Jasco P-3000 polarimeter. Optical rotations ([α]$_D$) were expressed in degrees per decimetre per centimetre (°/dm/cm). Optical rotations ([α]$_D$) were measured at 589 nm and were corrected for the path length of the sample cuvette. Analytical results for all compounds are given as the mean of three samples. The mass spectra were obtained using a Shimadzu GCMS-QP2010 (EI:70 eV, 70–550 m/z) mass spectrometer. HRMS (ESI)/HRMS (APCI) mass spectra were recorded on an LC-MS-2010A (Shimadzu). HRMS data were calibrated using a Shimadzu LC-MS-2010A (EI:70 eV, 70–550 m/z). Chemical structures were confirmed by single-crystal X-ray diffraction analysis. Infrared spectra were recorded using a Perkin-Elmer Spectrum 1000 infrared spectrophotometer.

3.1 Bromobenzene

To a solution of 4-fluoro-1,2-dimethoxybenzene (1.00 mL, 7.62 mmol) in CH$_2$Cl$_2$ (15 mL) was added Br$_2$ (0.45 mL, 8.7 mmol) at rt. After stirring for 5 h, the reaction was stopped by adding sat. aq NaHCO$_3$ and aq 10% Na$_2$S$_2$O$_3$. The crude products were extracted with CH$_2$Cl$_2$ (3 ×), and the combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (140 °C (oven temp)/7.4 mmHg) to afford bromobenzene (1.84 g, quant) as a colorless oil; R$_f$ = 0.72 (hexane/EtOAc 2:1).

IR (ATR): 3004, 2937, 2360, 1601, 1506, 1439, 1389, 1263, 1215, 1162 cm$^{-1}$.

1H NMR (600 MHz, DMSO-$_d_6$): δ = 2.48 (s, 3 H), 2.78 (br s, 1 H, OH), 4.38 (dd, J = 10.8, 3.6 Hz, 1 H), 4.44 (d, J = 10.8 Hz, 1 H), 4.76 (dd, J = 4.8, 3.6 Hz, 1 H), 5.06 (d, J = 4.8 Hz, 1 H), 7.40 (d, J = 7.8 Hz, 2 H), 7.90 (d, J = 7.8 Hz, 2 H).

13C NMR (150 MHz, DMSO-$_d_6$): δ$_{C}$ = 21.8, 68.1, 71.2, 74.3, 128.4, 130.2, 131.6, 146.3, 168.5.


3.2 Tosylate

To a solution of diol 14 (4.00 g, 33.9 mmol) in pyridine (16 mL) was added TsCl (7.10 g, 72.2 mmol) at 0 °C. After stirring for 14 h, the pH of the reaction was adjusted to 1 by adding aq 6 M HCl. The crude product was extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by recrystallization with CH$_2$Cl$_2$ (3 ×) to afford tosylate 15 (6.55 g, 76%) as a white solid; R$_f$ = 0.72 (hexane/EtOAc 2:1).

IR (ATR): 3470, 1772, 1375, 1192, 1174, 1070, 1024, 816, 776 cm$^{-1}$.

1H NMR (600 MHz, CDCl$_3$): δ = 2.48 (s, 3 H), 2.78 (br s, 1 H, OH), 4.38 (dd, J = 10.8, 3.6 Hz, 1 H), 4.44 (d, J = 10.8 Hz, 1 H), 4.76 (dd, J = 4.8, 3.6 Hz, 1 H), 5.06 (d, J = 4.8 Hz, 1 H), 7.40 (d, J = 7.8 Hz, 2 H), 7.90 (d, J = 7.8 Hz, 2 H).

13C NMR (150 MHz, CDCl$_3$): δ$_{C}$ = 21.8, 68.1, 71.2, 74.3, 128.4, 130.2, 131.6, 146.3, 168.5.

HRMS (ESI): m/z calcd for C$_{12}$H$_{12}$O$_{6}$SNa [M + Na]$^+$: 295.02468; found: 295.02465.

3.3 Lactone

To a solution of tosylate 15 (4.03 g, 14.8 mmol) in MeCN (70 mL) was added K$_2$CO$_3$ (8.06 g, 58.3 mmol) at rt. After stirring for 22 h, the mixture was passed through a short column of SiO$_2$ and washed with MeCN. The solvent was removed in vacuo, and the residue was purified by bulb-to-bulb distillation (155 °C (oven temp)/24 mmHg) to afford epoxy lactone 16 (1.11 g, 75%) as a colorless oil; R$_f$ = 0.50 (CHCl$_3$/MeOH 19:1); [α]$_D$ = +28 (c 1.04, CHCl$_3$).

IR (neat): 3094, 2971, 1782, 1386, 1046, 953, 852, 783 cm$^{-1}$.

1H NMR (600 MHz, CDCl$_3$): δ = 2.38 (d, J = 2.6 Hz, 1 H), 4.22 (dd, J = 2.6, 1.5 Hz, 1 H), 4.32 (dd, J = 11.4, 1.5 Hz, 1 H), 4.47 (d, J = 11.4 Hz, 1 H).

13C NMR (150 MHz, CDCl$_3$): δ$_{C}$ = 49.6, 55.0, 68.3, 170.7.

Anal. Calcd for C$_8$H$_8$O$_4$: C, 48.20; H, 4.03; Found: C, 48.20; H, 4.03.
epoxyketone 19

To a solution of bromobenzene (8; 3.38 g, 14.4 mmol) in Et2O (60 mL) was added n-BuLi (1.55 M in hexane, 8.5 mL, 13 mmol) at −78 °C. After stirring for 1 h at −78 °C, a solution of epoxy lactone (16; 1.21 g, 12.1 mmol) in Et2O (60 mL) was added to the mixture, which was stirred for 1 h at −78 °C. The reaction was stopped by adding sat. aq NH4Cl. The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford ketone 28 (6.4 mg, 85%) as a white amorphous solid; Rf = 0.50 (hexane/EtOAc 1:1); [α]D20 = −122 (c 0.980, CHCl3).

IR (neat): 2917, 1673, 1609, 1513, 1456, 1348, 1309, 1197, 1091, 1040 cm−1.

1H NMR (600 MHz, CDCl3): δ = 1.29 (s, 3 H), 1.30 (s, 3 H), 3.12 (dd, J = 9.5, 3.7 Hz, 1 H), 3.14 (dd, J = 9.5, 3.7 Hz, 1 H), 3.35 (s, 3 H), 3.80 (s, 3 H), 3.83 (d, J = 3.1 Hz, 1 H), 4.18 (d, J = 12.0 Hz, 1 H), 4.61 (dd, J = 12.0, 3.1 Hz, 1 H), 4.72 (d, J = 3.7, 3.7 Hz, 1 H), 4.74 (d, J = 7.4 Hz, 1 H), 4.79 (d, J = 7.4 Hz, 1 H), 4.93 (dd, J = 3.1, 3.1 Hz, 1 H), 6.44 (s, 1 H), 6.48 (d, J = 8.6 Hz, 1 H) 6.76 (s, 1 H), 7.81 (d, J = 8.6 Hz, 1 H).

13C NMR (150 MHz, CDCl3): δ = 21.5, 22.7, 27.5, 46.6, 53.5, 55.9, 56.3, 62.3, 72.2, 76.9, 90.9, 91.4, 100.9, 104.9, 110.4, 113.2, 113.4, 129.8, 143.9, 147.4, 149.5, 167.5, 189.0.


To a mixture of 3-fluorophenol (3.38 g, 14.4 mmol) in Et2O (60 mL) was added n-BuLi (1.55 M in hexane, 8.5 mL, 13 mmol) at −78 °C. After warming to rt over 1 h, the reaction was stopped by adding sat. aq NaHCO3. The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 1:1) to afford ketone 19 (3.72 g, 83%) as a white solid. The mother liquor was concentrated in vacuo, and the residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford alcohol 27 (21.9 mg, 80%) as a white amorphous solid.

Alcohol 27

To a solution of ether (20.1 mg, 0.0346 mmol) in THF (1 mL) was added tert-butylchloromethyl chloride (2.07 g, 13.7 mmol) and imidazole (1.67 g, 24.5 mmol) were added. After stirring for 1 h, the reaction was stopped by adding phosphate buffer (pH 7). The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was dissolved in DMF (60 mL), to which tert-butylimidethylsilyl chloride (2.67 g, 13.7 mmol) was added. After stirring for 1 h, the crude products were extracted with EtOAc (4 ×) to afford epoxy ketone 19 (3.72 g, 83%; total yield: 94%) as a white solid; mp 98–99 °C (EtOH); Rf = 0.56 (hexane/EtOAc 3:1); [α]D20 = +70.1 (c 1.15, CHCl3).

IR (ATR): 2954, 2930, 2856, 1681, 1611, 1514, 1464, 1450, 1272, 1223, 1142, 1094, 837 cm−1.

1H NMR (600 MHz, CDCl3): δ = 2.47 (s, 3 H), 2.70 (s, 3 H), 3.64 (d, J = 8.6 Hz, 1 H), 4.54 (d, J = 6.5 Hz, 1 H).

Alcohol 22

To a mixture of 3-fluorophenol (3.38 g, 14.4 mmol) in THF (1 mL) was added n-BuLi (1.55 M in hexane, 8.5 mL, 13 mmol) at −78 °C. After stirring for 1 h, the reaction was quenched by adding phosphate buffer (pH 7). The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 2:1 to 1:1) to afford alcohol 22 (194 mg, 98%) as a white amorphous solid.

Alcohol 23

To a solution of ether (20.1 mg, 0.0346 mmol) in t-BuOH (0.85 mL). THF (0.85 mL), and H2O (0.17 mL) was added ASCA-2 type Pd/C [10% Pd(OH)2/C, 110.4 (d, J = 12.0 Hz, 1 H)], 130.0 (d, J = 9.8 Hz, 1 H), 158.4 (d, J = 12.0 Hz, 1 C), 163.5 (d, J = 243 Hz, 1 C).

IR (neat): 2945, 2875, 1611, 1593, 1488, 1261, 1138, 1038, 975 cm−1.

1H NMR (600 MHz, CDCl3): δ = 15.74–15.64 (m, 1 H), 1.64–1.75 (m, 2 H), 1.80–1.94 (m, 2 H), 1.95–2.08 (m, 2 H), 3.58–3.68 (m, 1 H), 3.81–3.94 (m, 1 H), 6.64 (d, J = 8.6 Hz, 1 H) 6.79 (d, J = 8.3 Hz, 1 H), 6.79 (d, J = 8.3 Hz, 1 H), 6.83 (d, J = 8.3 Hz, 1 H), 7.21 (dd, J = 8.3, 8.3 Hz, 1 H).

Synthesis 2019, 51, 1139–1156


1151

Feature
tracted with EtO (3 ×), and the combined organic extracts were washed with H2O (2 ×) and brine, dried (Na2SO4), and concentrated in vacuo. The residue was dissolved in EtOH (1 mL), to which PPTS (27.0 mg, 0.107 mmol) was added at rt. The reaction mixture was warmed to −50 °C over 1 h, and the reaction was stopped by adding sat. aq NaHCO3. The crude product was extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by flash column chromatography (SiO2, hexane/ETOAc 9:1) to afford epoxy alcohol 35 (152 mg, 85%) as a white amorphous solid; Rf = 0.70 (hexane/ETOAc 2:1); [α]D 20 +24 (c 0.990, CHCl3).

IR (neat): 3497, 2954, 2931, 1619, 1513, 1405, 1259, 1222, 1117, 837 cm−1.
1H NMR (600 MHz, CDCl3): δ = −0.01 (s, 3 H), 0.02 (s, 3 H), 0.85 (s, 9 H), 1.40 (s, 3 H), 1.42 (s, 3 H), 3.24 (ddd, J = 6.9, 4.9, 2.7 Hz, 1 H), 3.48 (dd, J = 12.6, 2.7 Hz, 1 H), 3.66 (ddd, JCHF = 1.5 Hz, 1 H, OH), 3.80 (ddd, J = 12.6, 6.9 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.01 (dd, J = 4.9 Hz, JCHF = 4.9 Hz, 1 H), 5.64 (d, J = 10.0 Hz, 1 H), 6.46 (d, J = 8.6 Hz, 1 H), 6.54 (d, J = 10.0 Hz, 1 H), 6.60 (d, JCHF = 12.0 Hz, 1 H) 6.78 (ddd, J = 8.6 Hz, JCHF = 8.6 Hz, 1 H), 7.12 (d, JCHF = 7.0 Hz, 1 H).
13C NMR (150 MHz, CDCl3): δ = −53.3, −51.1, 18.4, 26.0, 28.0, 28.2, 56.3, 56.5, 59.6, 61.1, 61.8 (d, JCF = 7.5 Hz, 1 C), 71.9 (d, JCF = 3.9 Hz, 1 C), 76.8, 100.2 (d, JCF = 28.7 Hz, 1 C), 109.8 (d, JCF = 60.6 Hz, 1 C), 110.7 (d, JCF = 19.0 Hz, 1 C), 111.4 (d, JCF = 2.9 Hz, 1 C), 115.1 (d, JCF = 6.1 Hz, 1 C), 120.4 (d, JCF = 15.0 Hz, 1 C), 124.8 (d, JCF = 12.0 Hz, 1 C), 127.3 (d, JCF = 4.5 Hz, 1 C), 131.1, 145.3 (d, JCF = 2.2 Hz, 1 C), 149.4 (d, JCF = 10.5 Hz, 1 C), 153.2 (d, JCF = 232.5 Hz, 1 C), 154.0, 156.4 (d, JCF = 250.5 Hz, 1 C).
19F NMR (565 MHz, CDCl3): δ = −120.4.
HRMS (ESI): m/z calcd for C40H32F8O3Si [M + H]+: 549.24785; found: 549.24903.

Ether 34
To a solution of phenol 33 (302 mg, 1.68 mmol) in EtOH (16.6 mL) was added CuCl2 (113 mg, 0.850 mmol) and PdCl2 (45.0 mg, 0.254 mmol) at rt. After stirring for 6 h at 0 °C, the reaction mixture was filtered through a Celite pad (washed with Et2O) and the filtrate was concentrated in vacuo. The residue was dissolved in THF (76 mL), to which Bu2AlH (1.0 M in hexane, 11.4 mL, 11.4 mmol) was added at −78 °C. After stirring for 40 min at −78 °C, the reaction was stopped by adding sat. aq Rochelle’s salt. After stirring for 40 min at rt, the crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was dissolved in THF (76 mL), to which i-BuAlH (1.0 M in hexane, 11.4 mL, 11.4 mmol) was added at −78 °C. After stirring for 20 min at −78 °C, the reaction was stopped by adding sat. aq Rochelle’s salt. After stirring for 40 min at rt, the crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO2, hexane/ETOAc 1:2) to afford diol 37 (1.85 g, 88%) as a white amorphous solid; Rf = 0.42 (hexane/ETOAc 2:1); [α]D 20 +111 (c 1.60, CHCl3).

IR (neat): 3476, 2930, 2857, 1624, 1577, 1513, 1465, 1448, 1257, 1116 cm−1.
1H NMR (600 MHz, CDCl3): δ = −0.03 (s, 3 H), −0.01 (s, 3 H), 0.84 (s, 9 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 2.72 (br s, 1 H, OH), 3.05 (br s, 1 H, OH), 3.28 (dd, J = 10.8, 8.2 Hz, 1 H), 3.42 (ddd, J = 5.7, 3.5 Hz, 1 H), 3.51 (dd, J = 10.8, 4.1 Hz, 1 H), 3.81 (s, 3 H), 3.88 (s, 3 H), 4.02–4.17 (m, 1 H), 5.49 (ddd, J = 5.7, JCHF = 2.5 Hz, 1 H), 5.64 (d, J = 10.0 Hz, 1 H), 6.44 (d, J = 8.4 Hz, 1 H), 6.47 (d, JCHF = 11.1 Hz, 1 H), 6.57 (d, J = 10.0 Hz, 1 H), 6.89 (ddd, J = 8.4 Hz, JCHF = 8.4 Hz, 1 H), 7.33 (d, J = 6.7 Hz, 1 H).
13C NMR (150 MHz, CDCl3): δ = −54.6, −53.3, 18.3, 25.9, 27.7, 28.0, 43.9 (br s, 1 C), 56.0, 56.5, 65.7, 70.5, 74.2, 76.5, 99.3 (d, JCF = 30.0 Hz, 1 C), 109.6 (d, JCF = 18.8 Hz, 1 C), 112.0 (d, JCF = 2.8 Hz, 1 C), 113.7 (d, JCF = 4.9 Hz, 1 C), 114.3 (d, JCF = 15.0 Hz, 1 C), 115.4 (d, JCF = 5.7 Hz, 1 C), 121.0 (d, JCF = 13.5 Hz, 1 C), 127.6 (d, JCF = 6.1 Hz, 1 C), 130.8 (d, JCF = 2.1 Hz, 1 C), 144.9 (d, JCF = 2.5 Hz, 1 C), 148.6 (d, JCF = 10.0 Hz, 1 C), 153.2 (d, JCF = 6.9 Hz, 1 C), 155.5 (d, JCF = 248.4 Hz, 1 C), 156.1 (d, JCF = 237.5 Hz, 1 C).
19F NMR (565 MHz, CDCl3): δ = −132.1, −131.4.

Diol 37
To a solution of epoxide alcohol 35 (2.09 g, 3.81 mmol) in CH2Cl2 (70 mL) was added BF3·OEt2 (126 mg, 0.888 mmol) in CH2Cl2 (6.2 mL) at −15 °C. After stirring for 40 min, the reaction was stopped by adding sat. aq NaHCO3. The crude product was extracted with CH2Cl2 (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was dissolved in THF (76 mL), to which i-BuAlH (1.0 M in hexane, 11.4 mL, 11.4 mmol) was added at −78 °C. After stirring for 20 min at −78 °C, the reaction was stopped by adding sat. aq Rochelle’s salt. After stirring for 40 min at rt, the crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO2, hexane/ETOAc 1:2) to afford diol 37 (1.85 g, 88%) as a white amorphous solid; Rf = 0.42 (hexane/ETOAc 2:1); [α]D 20 +111 (c 1.60, CHCl3).
**Alcohol 38**

To a solution of diol 37 (1.96 g, 3.56 mmol) in CH₂Cl₂ (12 mL) was added p-methoxybenzaldehyde dimethyl acetal (1.8 mL, 11 mmol) and PPTS (183 mg, 0.728 mmol) at rt. After stirring for 3.5 h, the reaction was stopped by adding sat.aq NaHCO₃. The crude product was extracted with CH₂Cl₂ (3 ×), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was passed through a silica gel column (hexane/EtOAc 5:1) to afford the crude product contaminated with p-methoxybenzaldehyde dimethyl acetal and p-methoxybenzaldehyde (as assessed by 1H NMR analysis). The mixture was dissolved in THF (18 mL) to which n-Bu₄NF (1.0 M in THF, 10.7 mL, 10.7 mmol) was added at rt. After stirring for 1 h, the reaction was stopped by adding phosphate buffer (pH 7). The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 2:1 to 1:1) to afford alcohol 38 (1.74 g, 89%) as a white amorphous solid; Rf = 0.55 (hexane/EtOAc 1:1); [α]D²⁰ +6.3 (c 0.815, CHCl₃).

**Alcohol 40**

To a solution of azetropically dried (toluene, 1 mL, 3 ×) ether 39 (189 mg, 0.354 mmol) in toluene (7.1 mL) was added i-Bu₂AlH (1.0 M in hexane, 1.05 mL, 1.05 mmol) at 0 °C. After stirring for 1 h, the reaction was stopped by adding sat. aq Rochelle’s salt. After stirring for 1.5 h at rt, the crude product was extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 4:1 to 2:1) to afford alcohol 40 (176 mg, 93%) as a white amorphous solid; Rf = 0.55 (hexane/EtOAc 1:1); [α]D²⁰ +6.3 (c 1.26, CHCl₃).

**Ether 39**

To a solution of azetropically dried (toluene, 1 mL, 3 ×) alcohol 38 (28.6 mg, 0.0516 mmol) in toluene (1.1 mL) was added t-BuOK (16.2 mg, 0.144 mmol) at rt. The reaction mixture was refluxed for 80 min. After cooling to rt, the reaction was stopped by adding sat. aq NH₄Cl. The crude product was extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford ether 39 (20.3 mg, 74%) as a colorless oil; Rf = 0.77 (hexane/EtOAc 1:1); [α]D²⁰ +44 (c 0.815, CHCl₃).

**Ether 41**

To a solution of azetropically dried (toluene, 1 mL, 3 ×) alcohol 40 (604 mg, 1.13 mmol) in toluene (50.6 mL) and DMPP (5.6 mL) were added 15-crown-5 ether (221 μL, 1.12 mmol) and NaH (822 mg, 63% dispersion in mineral oil, 2.16 mmol) at rt. After stirring for 2 h at 80 °C, the reaction was stopped by adding sat. aq NH₄Cl. The crude product was extracted with Et₂O (3 ×), and the combined organic extracts were washed with H₂O (3 ×) and brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 5:1 to 3:1) to afford ether 41 (552 mg, 95%) as a white amorphous solid; Rf = 0.67 (hexane/EtOAc 1:1); [α]D²⁰ +6.3 (c 0.865, CHCl₃); [α]D⁰ +17 (c 1.52, CHCl₃).

**HRMS (ESI):** m/z calcd for C₉H₈F₂O₃Si [M + H]+: 551.26350; found: 551.26466.

**Ether 39**

To a solution of diol 37 (1.96 g, 3.56 mmol) in CH₂Cl₂ (12 mL) was added p-methoxybenzaldehyde dimethyl acetal (1.8 mL, 11 mmol) and PPTS (183 mg, 0.728 mmol) at rt. After stirring for 3.5 h, the reaction was stopped by adding sat. aq NaHCO₃. The crude product was extracted with CH₂Cl₂ (3 ×), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was passed through a silica gel column (hexane/EtOAc 5:1) to afford the crude product contaminated with p-methoxybenzaldehyde dimethyl acetal and p-methoxybenzaldehyde (as assessed by 1H NMR analysis). The mixture was dissolved in THF (18 mL) to which n-Bu₄NF (1.0 M in THF, 10.7 mL, 10.7 mmol) was added at rt. After stirring for 1 h, the reaction was stopped by adding phosphate buffer (pH 7). The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 2:1 to 1:1) to afford alcohol 38 (1.74 g, 89%) as a white amorphous solid; Rf = 0.55 (hexane/EtOAc 1:1); [α]D²⁰ +6.3 (c 0.815, CHCl₃).

**Alcohol 40**

To a solution of azetropically dried (toluene, 1 mL, 3 ×) ether 39 (189 mg, 0.354 mmol) in toluene (7.1 mL) was added i-Bu₂AlH (1.0 M in hexane, 1.05 mL, 1.05 mmol) at 0 °C. After stirring for 1 h, the reaction was stopped by adding sat. aq Rochelle’s salt. After stirring for 1.5 h at rt, the crude product was extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 4:1 to 2:1) to afford alcohol 40 (176 mg, 93%) as a white amorphous solid; Rf = 0.55 (hexane/EtOAc 1:1); [α]D²⁰ +6.3 (c 1.26, CHCl₃).

**HRMS (ESI):** m/z calcd for C₁₀H₃₆F₂O₃Na [M + Na]+: 557.19460; found: 557.19289.
Alcohol 42 and Diol 43

To a solution of ether 41 (18.0 mg, 0.0348 mmol) and 2,6-di-tert-butylypyridine (40.2 mg, 0.210 mmol) in 1,4-dioxane (1.6 mL) and H2O (0.2 mL) was added DQ (24.2 mg, 0.107 mmol) at rt. After stirring for 1 h at 50 °C, the reaction was stopped by adding aq NaHCO3 and sat aq Na2S2O3. The crude materials were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford alcohol 42 as a white amorphous solid (10.0 mg, 72%) and diol 43 (1.6 mg, 11%) as a white amorphous solid, respectively.

42

\[ R_1 = 0.47 \text{(hexane/EtOAc 2:3); } [M + Na]^+ = 51 (c 0.560, CHCl}_3]. \]

IR (neat): 3461, 2973, 2930, 1511, 1462, 1221, 1194, 1146, 1090, 1016 cm⁻¹.

43

\[ R_1 = 0.39 \text{(hexane/EtOAc 1:2); } [M + Na]^+ = 106 (c 0.515, CHCl}_3]. \]

IR (neat): 3420, 2929, 1510, 1464, 1263, 1198, 1153, 1115, 1033, 755 cm⁻¹.

Tephrosin (3) via Oxidation of Diol 43

To a solution of diol 43 (17.7 mg, 0.0429 mmol) in DMSO (0.5 mL) was added IBX (49.5 mg, 0.177 mmol) at rt. After stirring for 5.5 h, the reaction was stopped by adding aq NaHCO3 and aq 10% Na2S2O3. The crude product was extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford (-)-deguelin [(2); 8.1 mg, 82%] as a yellow amorphous solid; \( R_1 = 0.63 \text{(hexane/EtOAc 1:1); } [M + Na]^+ = 395.14981; \) found: 395.14955.

Tephrosin (3) and 12a-epi-Tephrosin (44) via Oxidation of (--)-Deguelin (2) by IBX

To a solution of (--)-deguelin 2 (5.4 mg, 0.0214 mmol) in DMSO (0.5 mL) was added IBX (29.2 mg, 0.104 mmol) at rt. After stirring for 6.5 h, the reaction was stopped by adding aq NaHCO3 and aq 10% Na2S2O3. The crude product was extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford (--)-tephrosin (2; 2.4 mg, 44%) as a white amorphous solid and (+)-12a-epi-tephrosin (44; 2.4 mg, 44%) as a white solid.
(−)-Tephrosin (3)

| [a]_D^20 ~ 81 (c 0.18, CHCl_3). |

(−)-12a-epi-Tephrosin (44)

Mp 208–210 °C; R_f 0.51 (hexane/EtOAc 1:1); [a]_D^20 +2.6 × 10^2 (c 0.10, CHCl_3).

IR (neat) 3450, 1690, 1594, 1575, 1504, 1447, 1266, 1109, 1088 cm⁻¹.

Oxidation of (−)-Deguelin (2) by TBD and O_2

To a solution of (−)-deguelin (2; 7.0 mg, 0.018 mmol) in DMSO (0.6 mL) and CuO (0.6 mg, 0.004 mmol) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (4.5 mg, 0.032 mmol) at rt under O_2. After stirring for 4.5 h, the reaction was stopped by adding sat. aq NH_4Cl. The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford (±)-tephrosin (3; 3.9 mg, 53%) as a white amorphous solid and (−)-12a-epi-tephrosin (44; 2.0 mg, 27%) as a white solid.

Oxidation of (−)-Deguelin (2) by K_2Cr_2O_7

To a solution of (−)-deguelin (2; 4.8 mg, 0.012 mmol) in AcOH (0.25 mL) and H_2O (0.08 mL) was added K_2Cr_2O_7 (5.3 mg, 0.018 mmol) at 60 °C. After stirring for 30 min, the reaction was stopped by adding sat. aq NaHCO_3, and 10% aq Na_2S_2O_3. The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 3:2, 2 ×) to afford (−)-tephrosin (3; 4.7 mg, 94%) as a white amorphous solid; [a]_D^20 ~ 84 (c 0.23, CHCl_3).

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Supporting Information

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