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

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Dedicated to the memory of the late Professor Sho Ito
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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) $S_N$Ar 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, $S_N$Ar cyclization, total synthesis

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).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

R = H, R’ = H (–)-rotenone (1)
R = OH, R’ = H (–)-rotenolone
R = H, R’ = OH (–)-sumatrol
β-toxicarol
R = H, R = OH (–)-α-toxicarol
β-dehydrodeguelin
β-dehydrorotenone
dalpanol (4)
–dalpanol (4)
dehydrodeguelin
dehydrorotenone

1.2 Synthesis of Pinacols and Epoxides

The above-pinacol (5a) and epoxide (6) were prepared by benzylation and epoxidation of the respective alcohols (5b) and (6). The pinacols (5a) were hydrolyzed to the epoxides (6) by periodate oxidation. The hydrolysis products were isolated in pure form by column chromatography.
Their toxicity originates from the interference of the ubiquinone oxidoreductase of the respiratory electron transport chain.\(^1\) 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.\(^6\) On the other hand, significant reports have appeared on the antitumor effects of 2\(^7\) and 3,\(^7\) 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. Teruaki 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).1,8 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 methylations 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,9 1960), (±)-2 [(Fukami,10a,b 1960) and (Yamashita,10c 1974)], and (–)-1 (Yamashita,11 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.12 However, total synthesis reports have appeared as well, including (±)-2 [(Sames,10d 2003) and (Xu,10e 2018)], and (–)-2 [(Winssinger,11a 2010), (Scheidt,11b 2013), and (Suh,11c 2015)]. Approaches to tephrosin (–)-3 (Winssinger,11a 2010) and of (±)-3 (Xu,10e 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.14 The purpose of this paper is to outline our general synthetic approach, featuring the use of the group-selective, stereospecific 1,2-rearrangement of epoxy alcohol J followed by folding the product K into the tetracyclic scaffold L by dual S_NAr 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).

![Figure 3 Two aspects of semi-pinacol rearrangement](image)

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 stereochemistry (configuration/conformation) 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 Ia and Ib, 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 Ib, 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 stereochemistry of the reactants.

In 1957, Collins provided insight into the configurational 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 conformation 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 SN1 character, losing the stereochemical integrity. It was thus pointed out that the stereospecific 1,2-shift would become possible, if suitable conditions were set to achieve an internal SN2 process, which was indeed achieved as follows.

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

In 1983, we reported that chiral, non-racemic methane-sulfonyloxy 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 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 migratory 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 selective migration of the group of higher migratory aptitude by placing itself at the antiperiplanar position to the leaving group.

Equation 1  
\[ \text{Et}_3\text{Al-promoted pinacol-type rearrangement} \]

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 migratory aptitudes. Under carefully defined conditions to generate an aluminum alkoxide, a high group selectivity is observed as accounted by the chelation model. The 1,2-shift of alkyl groups is also stereospecific.

Equation 2  
\[ \text{Competition of two alkyl groups} \]

1.4.3 Epoxy Alcohol → Aldol Rearrangements

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 corresponding silyl ethers into aldol products.\(^ {21a}\) Later, we exploited the synthetic utility of the 1,2-shift-based aldol synthesis in various natural product syntheses.\(^ {21bc,22}\) Scheme 5 illustrates a divergent syntheses of antifungal natural products, avenaciolide and isoavenaciolide, featuring several important aspects of synthetic utilities.\(^ {21bc}\) 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, although 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 diastereomers 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 α-silylvinyl group has an excellent migratory aptitude, which was previously discovered in the pinacol-type rearrangement.\(^ {23}\) 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 discussed later.

Scheme 5  
\[ \text{Epoxy alcohol → aldol rearrangements and stereoselective reduction: divergent syntheses of avenaciolide and isoavenaciolide} \]

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 natural products, through which two powerful tactics relevant to the rotenoid synthesis have been developed.
Tactic #1 was the $S_nAr$ oxy-cyclization of aryl fluorides, working even without resorting to electron-withdrawing group(s), such as a nitro group (Equation 3). 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 enantio-meric 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).

As 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. 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 $S_nAr$ reactions. 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 $S_nAr$ oxy-cyclizations.

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. Fluorobenzene 6 was lithiated ($s$-BuLi, Et$_3$O, TMEDA, –78 °C, 1 h) and combined with chiral, non-racemic epoxy amide 5, giving epoxypiketone 7 in 72% yield. Bromide 8 was subjected to bromine–lithium exchange ($n$-BuLi, Et$_3$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.
Scheme 8 shows the key 1,2-rearrangement of epoxy alcohol 9. Upon treatment with BF$_3$·OEt$_2$ (CH$_2$Cl$_2$, 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 NaBH$_4$ 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 $^1$H 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.$^{21c}$

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 (CH$_2$OTBS). 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!’.

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, 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 H₂O₂ following an Organic Synthesis procedure (Na₂CO₃, H₂O, 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. Treatment of tosylate 15 with K₂CO₃ (MeCN, rt, 22 h) gave epoxy lactone 16 in 75% yield via the epimerization at C-2 followed by oxirane formation.

2.3 Synthesis of (−)-Rotenone (1)

Total synthesis of (−)-rotenone (1) was executed as follows: In comparison with our previous report, 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 H₂O₂ following an Organic Synthesis procedure (Na₂CO₃, H₂O, 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. Treatment of tosylate 15 with K₂CO₃ (MeCN, rt, 22 h) gave epoxy lactone 16 in 75% yield via the epimerization at C-2 followed by oxirane formation.

Bromobenzene 8 was treated with n-BuLi (Et₂O, −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 (TBSCI) and imidazole, giving siloxy ketone 19 in 94% yield (2 steps).

Ketone 19 is a common synthetic intermediate of our previous synthesis of 1 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.

Next, the DE-ring unit 6 was lithiated (s-BuLi, Et₂O, 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. Pleasingly, the reaction of epoxy alcohol 20 with BF₃·OEt₂ (20 mol%, CH₂Cl₂, 0 °C, 15 min) followed by the reaction with NaBH₄ 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. 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 S₅Ar oxy-cyclizations (Scheme 13). Upon treatment of 22 with n-Bu₅NF (THF, rt, 1 h), the TBS group was removed, giving alcohol 23 in 98% yield, ready for the S₅Ar 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)₂ (10 mol%) and PCy₃ (30 mol%) (toluene, reflux, 2 h), giving tetrahydropyran 24 in 86% yield. Upon treatment with AlH₃, anisylidene acetal 24 was regioselectively cleaved, giving alcohol 25 as a single isomer (79% yield). The S₅Ar oxy-cyclization of 25 proceeded smoothly (NaH, 15-crown-5, toluene,
Finally, treatment of 4 with Burgess reagent\textsuperscript{33} gave 1 in 50% yield. A side product, benzo furan 29, was obtained in 13% yield, arising most likely from the tertiary cation generation followed by a 1,2-hydr ide shift. Recrystallization from benzene gave 1 as color less crystals \([\text{mp 153–154 °C}, [\alpha]_D^{23} –1.5 \times 10^2 (c 0.070, \text{CHCl}_3)] \text{[Lit.}\textsuperscript{11} \text{mp 165–166 °C}, [\alpha]_D^{23} –177 (c 2, \text{CHCl}_3)]\). 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 \((^1\text{H and } ^{13}\text{C NMR, IR, HRMS})\textsuperscript{35}\).

### 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 THP 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\textsubscript{2}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 \(^1\text{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\%, \text{CH}_2\text{Cl}_2, –15 °C, 40 min). The crude material containing aldol 36 was immediately reduced with \text{i-Bu}_2\text{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 \text{i-Bu}_2\text{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$_\text{Ar}$ oxy-cyclizations (Scheme 16). The S$_\text{Ar}$ reaction of 38 proceeded smoothly by the action of i-Bu$_2$AlH (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$_\text{Ar}$ 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:[$^{39}$ $\alpha$)$_0$ = 46 (c 0.20, CHCl$_3$) [Lit. $^{40}$ $\alpha$)$_0$ = 45 (c 0.2, CHCl$_3$)].

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

As noted in the introduction, novel biological activities[$^7$] 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:[$^{40}$c $\alpha$)$_0$ = −86 (c 0.2, CHCl$_3$) [Lit. $^{40}$c $\alpha$)$_0$ = −98 (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: Russell\(^41\) used K\(_2\)Cr\(_2\)O\(_7\) for converting (–)-2, obtained from natural rotenone (–)-1, while Xu\(^10\) 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 [K\(_2\)Cr\(_2\)O\(_7\), AcOH, H\(_2\)O (3:1), 60 °C, 0.5 h], which cleanly gave (–)-3 in 94% yield [\([\alpha]_D^{20} –84 \ (c 0.23, \text{CHCl}_3)\) (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 O\(_2\) (1 atm) in the presence of Cu\(_2\)O and TBD (DMSO, rt, 4.5 h), a separable mixture of two products formed. After separation by preparative TLC (hexane/EtOAc 3:2), the less polar product (\(R_f = 0.65\)) was the desired product 3 (53% yield), while the more polar one (\(R_f = 0.51\)) 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 \([\alpha]_D\) 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 enantipure, [(d) and (e) in Figure 4]. This result could be explained by an intramolecular oxygen transfer (Equation 6), albeit with no diastereofacial selectivity.

**Figure 4** Assessment of ee for 3 and 44. Conditions for 3: CHIRALPAK\(^\circ\) IB (ø 4.6 mm × 250 mm), hexane/EtOAc (4:1); for 44: CHIRALPAK\(^\circ\) IF (ø 4.6 mm × 250 mm), hexane/EtOAc (3:2); flow rate: 1.0 mL/min, 25 °C, 254 nm.

In contrast, the result was markedly different with the Xu protocol (Table 1, entry 2). Upon exposure of (–)-2 to O\(_2\) (1 atm) in the presence of Cu\(_2\)O 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 (\(R_f = 0.65\)) was the desired product 3 (53% yield), while the more polar one (\(R_f = 0.51\)) 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 \([\alpha]_D\) 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.

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

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 enantipure, [(d) and (e) in Figure 4]. This result could be explained by an intramolecular oxygen transfer (Equation 6), albeit with no diastereofacial selectivity.
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$_2$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 (−)-deguinol and also its conversion into (−)-tephrosin and (+)-12α-e-pi-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 DMAP 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. $^1$H, $^{13}$C, and $^{19}$F NMR spectra (HRMS) were obtained with Bruker Daltonics micrOTOF-Q II. Chemical shifts ($\delta$) are expressed in parts per million (ppm) downfield from internal standard (TMS: $\delta = 0.00$) and hexafluorobenzene: $\delta = -164.9$), and coupling constants are reported in hertz (Hz). Standard abbreviations were used for splitting patterns. IR spectra were recorded on Thermo Scientific Nicolet iS5 FTIR spectrometer. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded by using Thermo Scientific i5 FTIR spectrophotometer equipped iDS ATR accessory. Optical rotations [α]$_D$ were measured on a Jasco P-3000 polarimeter. High-resolution mass spectra (HRMS) were obtained with Bruker Daltonics microOTOF-Q II. Syntheses and characterization data of compounds 1, 4–7, 9, 11, 12, 20–26, and 29 were reported in our previous paper.$^{14}$

bromobenzene 8

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 trituration with CH$_2$Cl$_2$ (3 ×) to afford diol 14 (3.15 g, quant) as a colorless oil; $R_f$ = 0.34 (hexane/EtOAc 2:1).

IR (ATR): 1530, 1442, 1248, 1191, 771 cm$^{-1}$.

$^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$ = 4.04 (d, $J$ = 9.9 Hz, 1 H), 4.23 (dd, $J$ = 4.7, 3.0 Hz, 1 H), 4.28 (dd, $J$ = 9.9, 3.0 Hz, 1 H), 4.37 (d, $J$ = 4.7 Hz, 1 H), 5.35 (br s, 1 H, OH), 5.76 (br s, 1 H, OH).

$^{13}$C NMR (150 MHz, DMSO-d$_6$): $\delta$ = 68.4, 69.5, 71.8, 176.4.


lactone 16

To a solution of lactone 15 (4.03 g, 14.56 mmol) in MeCN (70 mL) was added K$_2$CO$_3$ (8.06 g, 58.3 mmol) at rt. After stirring for 2 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 lactone 16 (1.11 g, 75%) as a colorless oil; $R_f$ = 0.50 (CHCl$_3$/MeOH 9:1); [α]$_D^{20}$ = +28 ($c$ 1.04, CHCl$_3$).

IR (neat): 1747, 1726, 1704, 1691, 1634, 1514, 1454, 1353, 1281, 1226, 1036, 890 cm$^{-1}$.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 4.30 (d, $J$ = 7.8 Hz, 2 H), 7.90 (d, $J$ = 7.8 Hz, 2 H), 7.90 (d, $J$ = 7.8 Hz, 2 H).

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 113.1, 122.7, 146.3, 147.6, 152.7, 155.8, 161.5, 168.1.

HRMS (ESI): m/z calcd for C$_{14}$H$_{12}$O$_4$: 295.02468; found: 295.0248; 295.0249.
products were extracted with Et2O (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-butylimidethylsilyle 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 H2O (2 ×) and brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 3:1) to afford alcohol 19 (3.27 g, 83%) as a white solid.

To a solution of acetal 22 (235 mg, 0.322 mmol) in THF (1.8 mL) was added n-BuLi (1.64 M in hexane, 0.40 mL, 0.66 mmol) at −78 °C. After stirring for 1 h, the reaction was quenched by adding sat. aq NH4Cl. The crude products were washed with Et2O (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]D = –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 (3, H), 1.30 (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 (3, H), 3.80 (3, H), 3.83 (J = 3.1 Hz, 1 H), 4.18 (J = 12.0 Hz, 1 H), 4.61 (J = 12.0, 3.1 Hz, 1 H), 4.72 (J = 3.7, 3.7 Hz, 1 H), 4.74 (J = 7.4 Hz, 1 H), 4.79 (J = 7.4 Hz, 1 H), 4.93 (J = 3.1, 3.1 Hz, 1 H), 6.44 (J = 12.0 Hz, 1 H), 6.48 (J = 8.6 Hz, 1 H), 6.76 (J = 8.6 Hz, 1 H), 7.81 (dd, J = 8.6 Hz, 1 H).
The combined organic extracts were washed with H$_2$O (2 ×) and brine, dried (Na$_2$SO$_4$), 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 60 °C and stirred for 3 h. The reaction was stopped by adding sat. aq NaHCO$_3$. 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 flash column chromatography (SiO$_2$, hexane/EtOAc 10:1) to afford phenol 33 (88.9 mg, 92%) as a colorless oil; $R_f$ = 0.34 (hexane/EtOAc 6:1).

IR (neat): 3497, 2954, 2931, 1619, 1513, 1405, 1259, 1222, 1117, 837 cm$^{-1}$.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 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, $J_{HF}$ = 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, $J_{HF}$ = 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, $J_{HF}$ = 12.0 Hz, 1 H) 6.78 (dd, $J$ = 8.6 Hz, $J_{HF}$ = 8.6 Hz, 1 H), 7.12 (d, $J_{HF}$ = 7.0 Hz, 1 H).

$^1$C NMR (150 MHz, CDCl$_3$): $\delta$ = 76.8, 100.2 (d, $J_{CF}$ = 28.7 Hz, 1 C), 109.8 (d, $J_{CF}$ = 60.0 Hz, 1 C), 110.7 (d, $J_{CF}$ = 19.0 Hz, 1 C), 111.4 (d, $J_{CF}$ = 2.9 Hz, 1 C), 115.1 (d, $J_{CF}$ = 6.1 Hz, 1 C), 120.4 (d, $J_{CF}$ = 15.0 Hz, 1 C), 124.8 (d, $J_{CF}$ = 12.0 Hz, 1 C), 127.3 (d, $J_{CF} = 4.5$ Hz, 1 C), 131.1, 145.3 (d, $J_{CF}$ = 2.2 Hz, 1 C), 149.4 (d, $J_{CF} = 10.5$ Hz, 1 C), 153.2 (d, $J_{CF}$ = 232.5 Hz, 1 C), 154.0, 156.4 (d, $J_{CF} = 250.5$ Hz, 1 C).

HRMS (ESI): $m/z$ calc for C$_3$H$_5$FO [M – H]: 179.08777; found: 179.08734.

ether 34

To a solution of phenol 33 (302 mg, 1.68 mmol) in EtOH (16.6 mL) was added CuCl$_2$ (113 mg, 0.850 mmol) and PdCl$_2$ (45.0 mg, 0.254 mmol) at rt. After stirring for 6 h at 60 °C, the reaction mixture was filtered through a Celite pad (washed with Et$_2$O) and the filtrate was concentrated to half its volume in vacuo. The crude products were added to aq 1 M NaOH. After extraction with hexane (3 ×), 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);20 mmHg) to afford ether 34 (220 mg, 74%) as a colorless oil; $R_f$ = 0.80 (hexane/EtOAc 6:1).

IR (neat): 2977, 2928, 1619, 1463, 1284, 1238, 1210, 1117, 1041, 754 cm$^{-1}$.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 1.44 (s, 6 H), 5.64 (d, $J$ = 9.8 Hz, 1 H), 6.52–6.59 (m, 3 H), 7.02 (ddd, $J$ = 11.5, 7.2 Hz, $J_{HF}$ = 7.2 Hz, 1 H).

$^1$C NMR (150 MHz, CDCl$_3$): $\delta$ = 29.7, 76.4, 107.3 (d, $J_{CF}$ = 21.0 Hz, 1 C), 110.0 (d, $J_{CF}$ = 18.2 Hz, 1 C), 112.1 (d, $J_{CF}$ = 3.1 Hz, 1 C), 115.1 (d, $J_{CF}$ = 4.7 Hz, 1 C), 128.9 (d, $J_{CF}$ = 10.3 Hz, 1 C), 130.7 (d, $J_{CF}$ = 2.5 Hz, 1 C), 154.0 (d, $J_{CF}$ = 7.0 Hz, 1 C), 158.6 (d, $J_{CF}$ = 248.1 Hz, 1 C).

HRMS (APCI): $m/z$ calc for C$_3$H$_5$FO [M + H]: 179.07212; found: 179.07276.

Epoxy Alcohol 35

To a solution of 34 (83.1 mg, 0.466 mmol) in Et$_2$O (4.0 mL) and N,N,N’,N’-tetramethylethylenediamine (0.4 mL) was added s-Buli (1.07 M in cyclohexane and hexane, 0.38 mL, 0.41 mmol) at –78 °C. After stirring for 1 h at –78 °C, a solution of azotropically dried (toluene, 1 mL 3 ×) epoxy ketone 19 (103 mg, 0.278 mmol) in Et$_2$O (1.5 mL) was added. The reaction mixture was warmed to –50 °C over 1 h, and the reaction was stopped by adding sat. aq NH$_4$Cl. The crude products were 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 flash column chromatography (SiO$_2$, hexane/EtOAc 9:1) to afford epoxy alcohol 35 (152 mg, 85%) as a white amorphous solid; $R_f$ = 0.70 (hexane/EtOAc 2:1); [a]$_{D}^{20}$ +24 (c 0.990, CH$_2$Cl$_2$).

IR (neat): 3497, 2954, 2931, 1619, 1513, 1405, 1259, 1222, 1117, 837 cm$^{-1}$.

HRMS (ESI): $m/z$ calc for C$_3$H$_5$FO$_2$Si [M + H]: 549.24785; found: 549.24903.
to afford the crude product contaminated with p-methoxybenzaldehyde dimethyl acetal and p-methoxybenzaldehyde (assayed 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 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]20D +26 (c 1.26, CHCl3).

IR (neat): 3484, 2930, 1617, 1512, 1464, 1214, 1197, 1116, 1045, 822 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 1.46 (s, 3.9 H), 1.47 (s, 3 H), 1.96 (d, J = 7.7 Hz, 1 H), 7.35 (m, 2 H), 7.39 (d, J = 7.7 Hz, 1 H), 7.81 (s, 1 H).

HRMS (ESI): m/z calcd for C31H33FO7Na [M + Na]⁺: 559.21025; found: 559.20992.

Alcohol 38
To a solution of diol 37 (1.96 g, 3.56 mmol) in CH2Cl2 (12 mL) was added t-BuOH (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]20D +26 (c 1.26, CHCl3).

IR (neat): 3484, 2930, 1617, 1512, 1464, 1214, 1197, 1116, 1045, 822 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 1.46 (s, 3 H), 1.47 (s, 3 H), 1.96 (d, J = 7.7 Hz, 1 H), 7.35 (m, 2 H), 7.39 (d, J = 7.7 Hz, 1 H), 7.81 (s, 1 H).
11.2 Hz, 1 H), 4.73 (d, J = 4.1 Hz, 1 H), 4.19 (d, J = 12.0 Hz, 1 H), 4.64 (dd, J = 12.1, 1.3 Hz, 1 H), 4.29 (dd, J = 4.1, 1.3 Hz, 1 H), 5.56 (d, J = 10.1 Hz, 1 H), 6.45 (d, J = 8.7 Hz, 1 H), 6.45 (d, J = 8.7 Hz, 1 H), 6.65 (d, J = 10 Hz, 1 H), 6.79 (s, 1 H), 7.75 (d, J = 8.7 Hz, 1 H).

13C NMR (150 MHz, CDCl3): δ = 28.2, 28.5, 44.4, 55.9, 56.3, 66.3, 72.4, 77.7, 100.9, 104.8, 109.1, 110.4, 111.5, 112.8, 115.8, 128.6, 128.7, 143.9, 147.4, 149.5, 157.0, 160.1, 189.2.


Tephrin (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 sat. 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 (−)-tephrin (3; 14.5 mg, 82%) as a white amorphous solid; Rf = 0.65 (hexane/EtOAc 1:1); [α]D290 –98° (c 0.20, CHCl3).

IR (neat): 3455, 1673, 1598, 1578, 1510, 1443, 1331, 1272, 1202, 1111, 1090, 1028 cm–1.

1H NMR (600 MHz, CDCl3): δ = 1.39 (s, 3 H), 1.45 (s, 3 H), 3.73 (s, 3 H), 3.82 (s, 3 H), 4.42 (s, 1 H, OH), 4.50 (dd, J = 12.1, 1.1 Hz, 1 H), 4.57 (dd, J = 2.5, 1.1 Hz, 1 H), 4.63 (dd, J = 12.1, 2.5 Hz, 1 H), 5.56 (d, J = 10.1 Hz, 1 H), 6.47 (d, J = 8.7 Hz, 1 H), 6.48 (s, 1 H, 6.56 (s, 1 H), 6.60 (d, J = 10 Hz, 1 H), 7.73 (d, J = 8.7 Hz, 1 H).

13C NMR (150 MHz, CDCl3): δ = 28.3, 28.5, 55.9, 56.4, 63.9, 67.4, 76.3, 78.0, 101.1, 108.6, 109.1, 110.4, 111.1, 111.9, 115.4, 128.6, 128.8, 144.0, 148.4, 151.1, 156.7, 160.8, 191.4.


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

To a solution of (−)-deguelin (2; 5.4 mg, 0.0144 mmol) in DMSO (0.5 mL) was added IBX (15.4 mg, 0.0550 mmol) at rt. After stirring for 5 h at 60 °C, the reaction mixture was warmed to 80 °C. The stirring was continued for 14 h, and then the reaction was stopped by adding sat. aq NaHCO3 and aq 10% Na2S2O3. 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 (−)-tephrin (3; 2.4 mg, 44%) as a white amorphous solid and (+)-12a-epi-tephrin (44; 2.4 mg, 44%) as a white solid.
Oxidation of (-)-Deguelin (2) by TBD and O2

To a solution of (-)-deguelin (2; 7.0 mg, 0.018 mmol) in DMSO (0.6 mL) and C6H6 (0.6 mmol) was added 1.57-triazacyclononane (4.4 mol) at rt under O2. After stirring for 4.5 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 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 K2Cr2O7

To a solution of (-)-deguelin (2; 4.8 mg, 0.012 mmol) in AcOH (0.25 mL) and H2O (0.08 mL) was added K2Cr2O7 (5.3 mg, 0.018 mmol) at 60 °C. After stirring for 30 min, the reaction was stopped by adding sat. aq NaHCO3 and aq 10% Na2S2O3. The crude products were extracted with EtOAc (3 ×), and the combined organic extracts were washed with brine (Na2SO4), 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; [α]D20 -81 (c 0.18, CHCl3).

References


(26) (a) Harris, J. M.; Neustadt, B. R.; Hao, J.; Stamford, A. W. Patent WO2009111449, 2009. (b) The original procedure employed Fe(III) as the catalyst, which was too reactive, leading to over-reaction (see experimental section).


(28) (a) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* 1985, 63, 127. (b) By modifying the purification protocol, the yield was substantially improved (65 → 94%).


(30) (a) Kvíčala, J.; Vlasáková, R.; Plocar, J.; Paleta, O.; Pelter, A. *Collect. Czech. Chem. Commun.* 2000, 65, 772. (b) The original procedure (using KF only) led to an incomplete reaction; full conversion was achieved by using K2CO3 as a base.


(35) A sample of (–)-I was purchased from Sigma-Aldrich.


(43) 3: $|\alpha|_{33}^{[2]} - 4.7 (c 0.20, CHCl3); 44: $|\alpha|_{23}^{[2]} + 1.1 (c 0.10, CHCl3).