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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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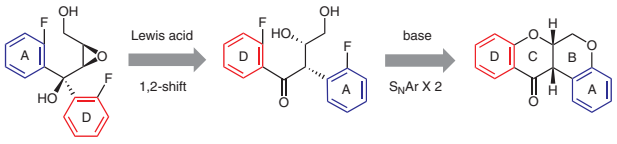

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Abstract A general synthetic approach to rotenoids is described, featuring 1) stereospecific, group-selective 1,2-rearrangements of epoxy alcohols, and 2) S_NAr oxy-cyclizations of aryl fluorides. The common intermediate epoxyketone, en route to (–)-rotenone 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

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 Clark[5c] 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'.

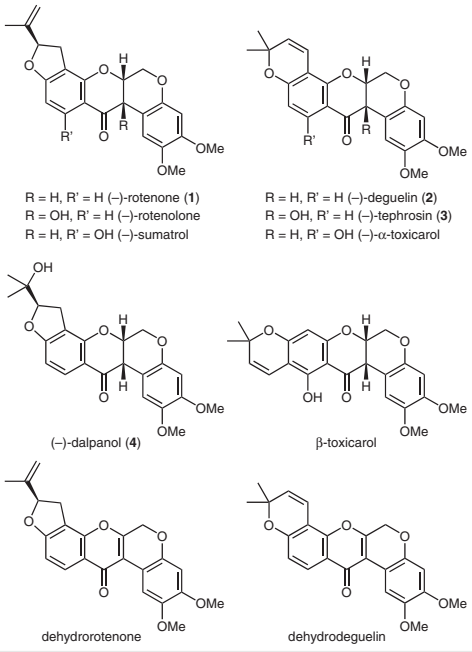
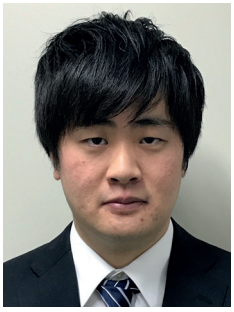


Figure 1 Natural rotenoids

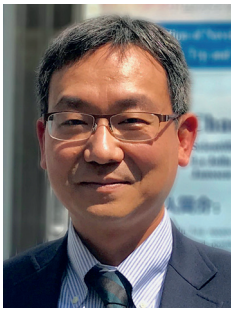
Their toxicity originates from the interference of the ubiquinone oxidoreductase of the respiratory electron transport chain.[1] Upon ingestion, the compounds are relatively innocuous to mammals, being rapidly metabolized, while fish and insects lack such a detoxification mechanism. Frightening enough, 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**[7a] and **3**,[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 GlyTech. 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).

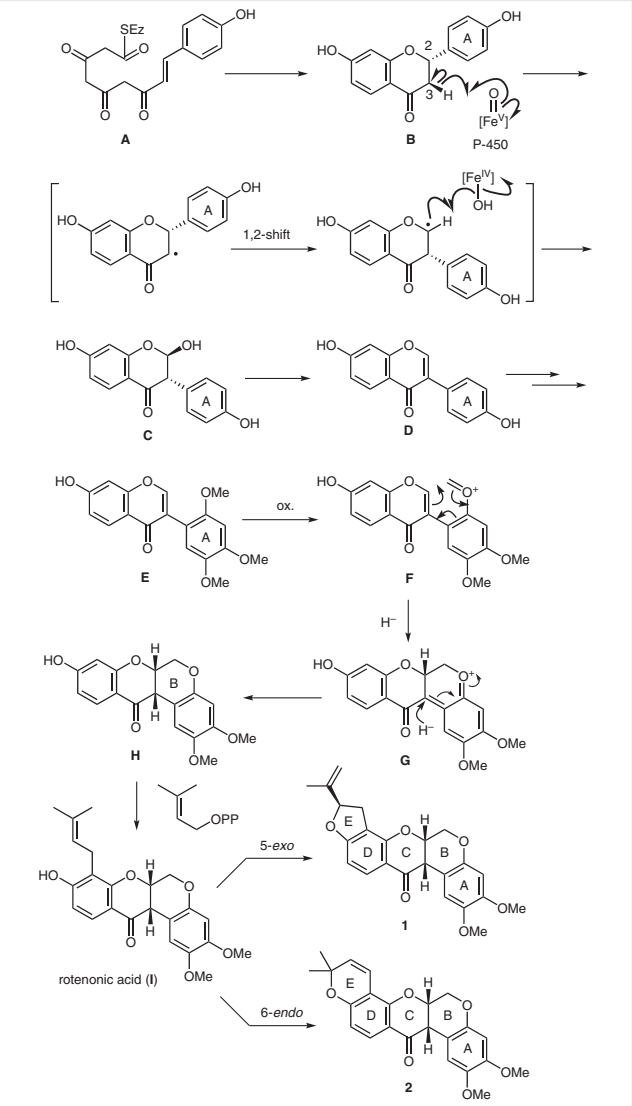
Figure 2 Prof. C.-C. Liao, Taiwan, shows roten plant, recalling his childhood

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 isoflavanone **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.

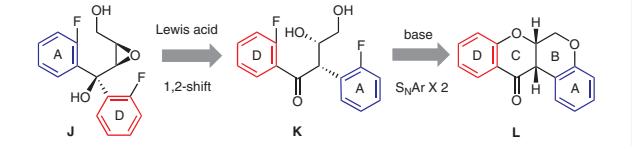
1.3 Synthetic Studies

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,[13a] 2010), (Scheidt,[13b] 2013), and (Suh,[13c] 2015)]. Approaches to tephrosin (–)-**3** (Winssinger,[13a] 2010) and of (±)-**3** (Xu,[10e] 2018) have appeared as well.



Scheme 1 Rotenoid biosynthesis

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-rearrangements 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).



Scheme 2 Our synthetic approach to rotenoids

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).

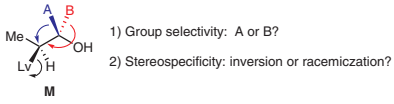


Figure 3 Two aspects of semi-pinacol rearrangement

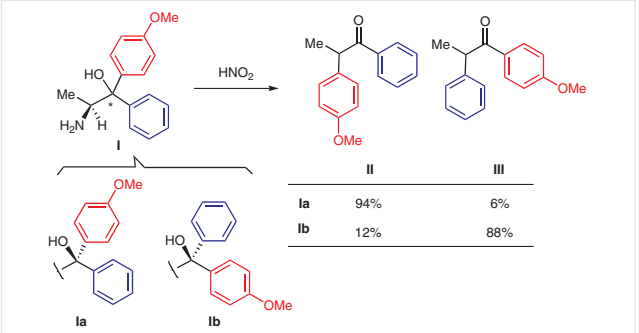
The *group selectivity* refers to the selectivity, among the two potential migrating groups, A and B, which undergoes the 1,2-shift. Two factors are relevant, namely a) migratory aptitudes of A and B, and b) effect of the stereochemistry of the reactant **M**.

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

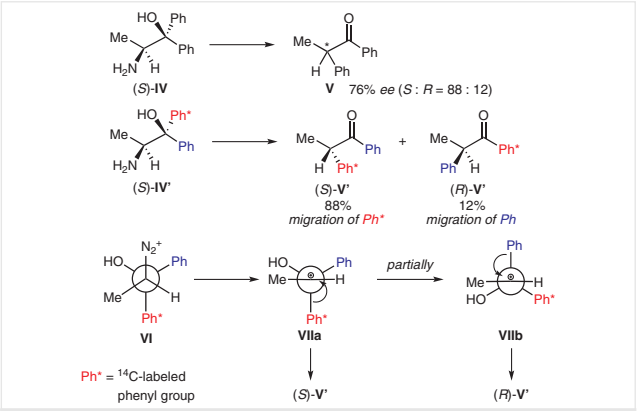
Around 1950, Curtin published the pioneering work[15] on the effect of the stereochemistry (conformation/configuration) of reactants on the reactivity (Scheme 3). Deaminative semi-pinacol rearrangement was the subject that led him to a concept, later called as the Curtin–Hammett principle.[16] Diastereomeric amino alcohols **Ia** and **Ib**, upon diazotization, gave markedly different product distributions. While **Ia** mostly gave **II** by the anisyl shift, and a minor amount of **III** was formed by the 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,[17] which clearly shows the importance of the stereochemistry of the reactants.

In 1957, Collins provided insight into the conformational factor using ingeneously designed tracer experiments (Scheme 4).[18] 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 ^{14}C-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



Scheme 3 Curtin's experiments

reaction proceeds via an open carbenium ion, which does not last long enough for the free bond roation around the C–C bond. Reflecting the most stable conformer 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*).



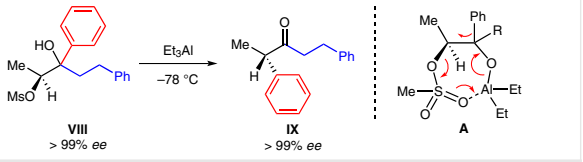
Scheme 4 Collins' experiments

Overall, due to the super-leaving ability of N_2 from aliphatic diazonium salts, the reaction takes on a typical S_N1 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 S_N2 process, which was indeed achieved as follows.

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

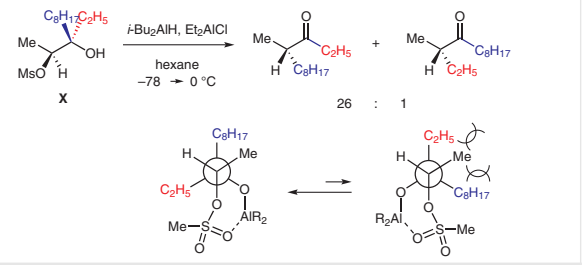
In 1983, we reported that chiral, non-racemic methanesulfonyloxy alcohol **VIII**, upon treatment with Et_3Al as a Lewis acid, undergoes stereospecific 1,2-rearrangement with inversion of the pre-existing stereogenic center (Equation 1).[19] Importantly, even when the the starting material is a diastereomeric 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 Et_3Al-promoted pinacol-type rearrangement

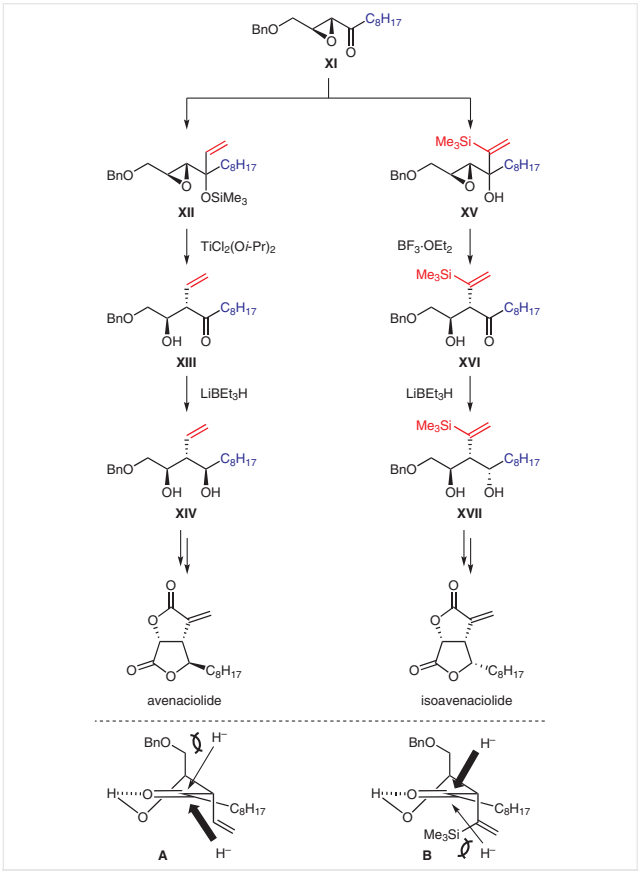
On the other hand, Equation 2 exemplifies a reaction where the *tert*-alcohol stereogenic center is decisive for the group selectivity.[20] Note that the potential migrating groups, ethyl and octyl, are of essentially the same migratory aptitudes. Under carefully defined conditions to generate an aluminum 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 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.[21b,c,22] Scheme 5 illustrates a divergent syntheses of antifungal natural products, avenaciolide and isoavenaciolide, featuring several important 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, 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.



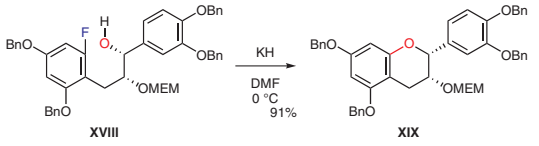
Scheme 5 Epoxy alcohol → aldol rearrangements and stereoselsective reduction: divergent syntheses of avenaciolide and isoavenaciolide

2 Results and Discussion

2.1 Synthetic Planning – A Thought Process

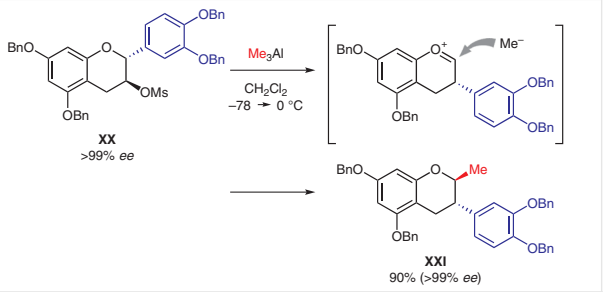
In the following, the thought process how our synthetic plan evolved will be described. The starting point was our recent study on the flavonoid- and isoflavonoid-class natural products, through which two powerful tactics relevant to the rotenoid synthesis have been developed.

Tactic #1 was the S_NAr oxy-cyclization of aryl fluorides,[24] working even without resorting to electron-withdrawing group(s), such as a nitro group (Equation 3).[24b]



Equation 3 Tactic #1: S_NAr oxy-cyclization of aryl fluorides

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.

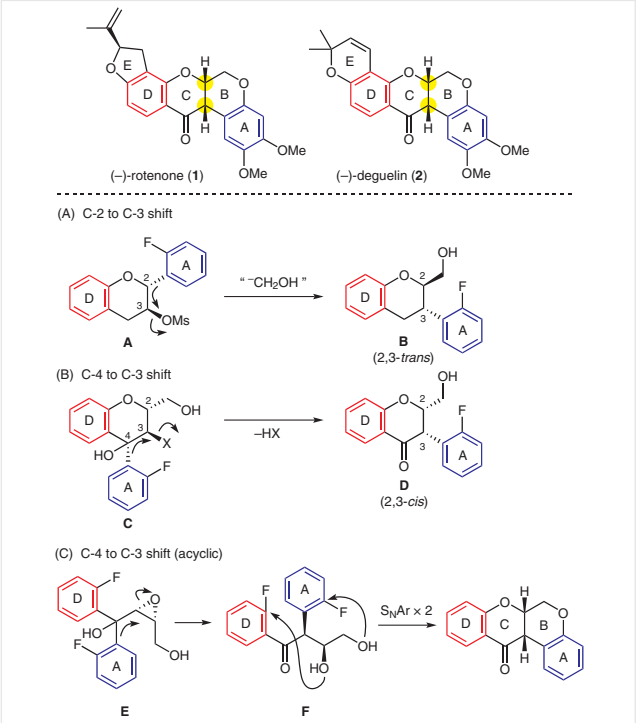


Equation 4 Tactic #2: 1,2-Shift approach to isoflavonoids

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 '$^-CH_2OH$' 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_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.

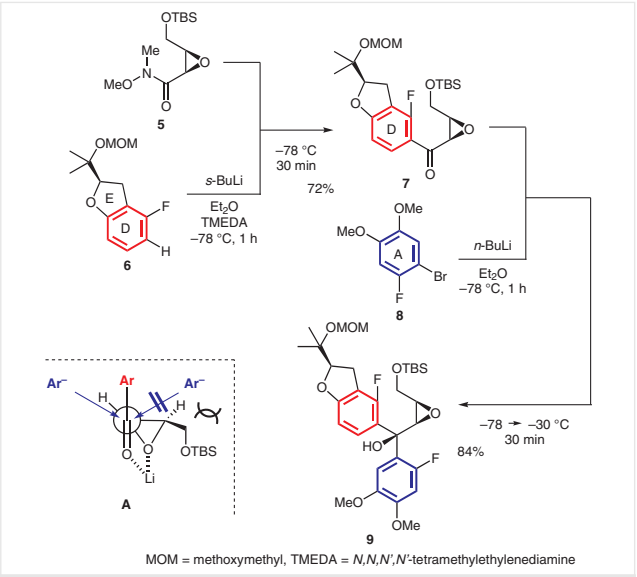


Scheme 6 Thought process

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]

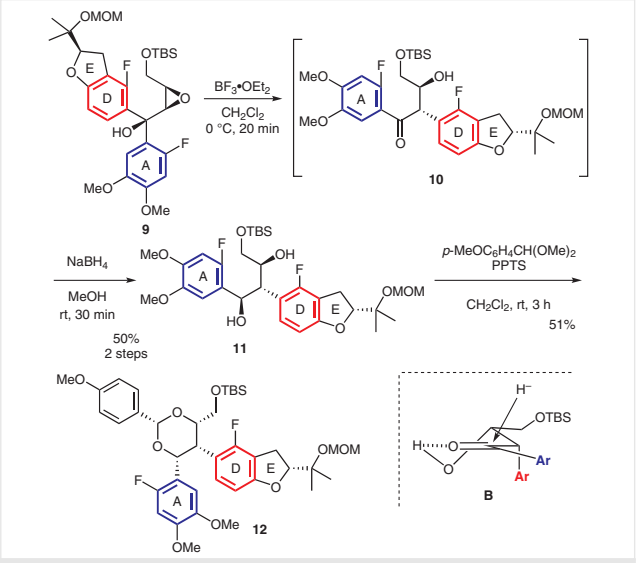
2.2 Preliminary Study on 1,2-Rearrangement

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_2O, TMEDA, –78 °C, 1 h) and combined with chiral, non-racemic epoxy amide **5**, giving epoxyketone **7** in 72% yield. Bromide **8**[26] was subjected to bromine–lithium exchange (*n*-BuLi, Et_2O, –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.[27]



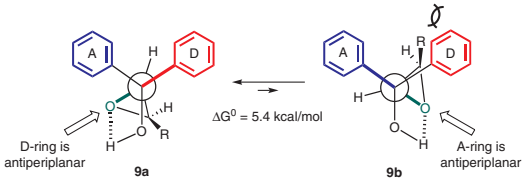
Scheme 7 Preliminary experiment 1 (substrate preparation)

Scheme 8 shows the key 1,2-rearrangement of epoxy alcohol **9**.[14] Upon treatment with $BF_3{\cdot}OEt_2$ (CH_2Cl_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 ^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**.[21c]



Scheme 8 Preliminary experiment 2 (1,2-shift/reduction)

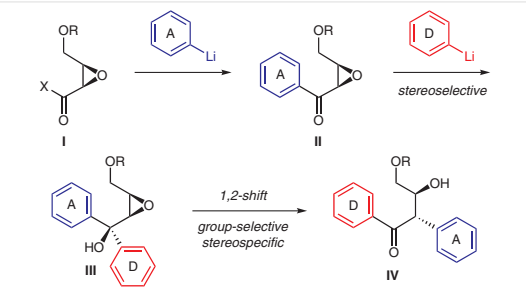
Even though the undesired isomer was obtained, the *perfect group selectivity* gave us valuable insight. Scheme 9 shows two hydrogen-bonded conformers of epoxy alcohol **9**, where conformer **9b** is disfavored by steric hindrance caused by the *cis*-substituent R (CH_2OTBS). Conformer **9a** would 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.



Scheme 9 Rationale for the group-selectivity

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,[16] 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 **II** 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.



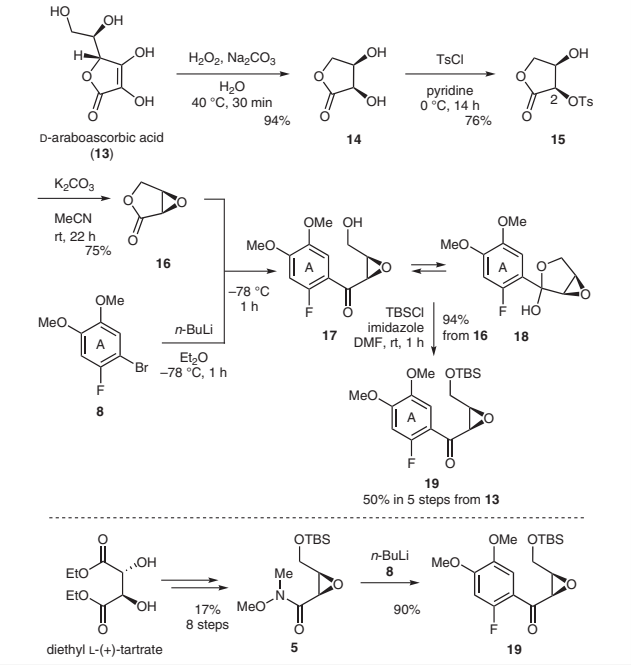
Scheme 10 Guideline for the group-selective 1,2-shift

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,[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,[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_2O_2 following an *Organic Synthesis* procedure[28] (Na_2CO_3, H_2O, 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.[29] Treatment of tosylate **15** with K_2CO_3 (MeCN, rt, 22 h) gave epoxy lactone **16** in 75% yield via the epimerization at C-2 followed by oxirane formation.[30]

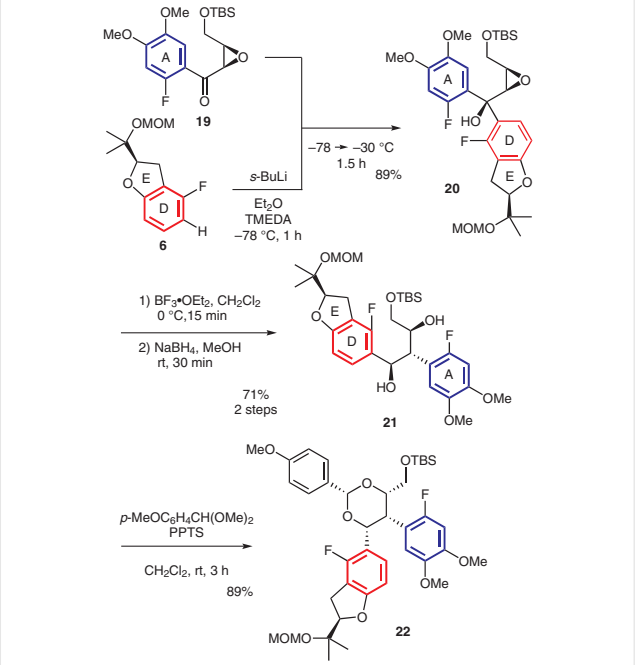


Scheme 11 Improved preparation of key intermediate **17**

Bromobenzene **8** was treated with *n*-BuLi (Et_2O, –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*-butyldimethylsilyl 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**[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-tartrate.[14]

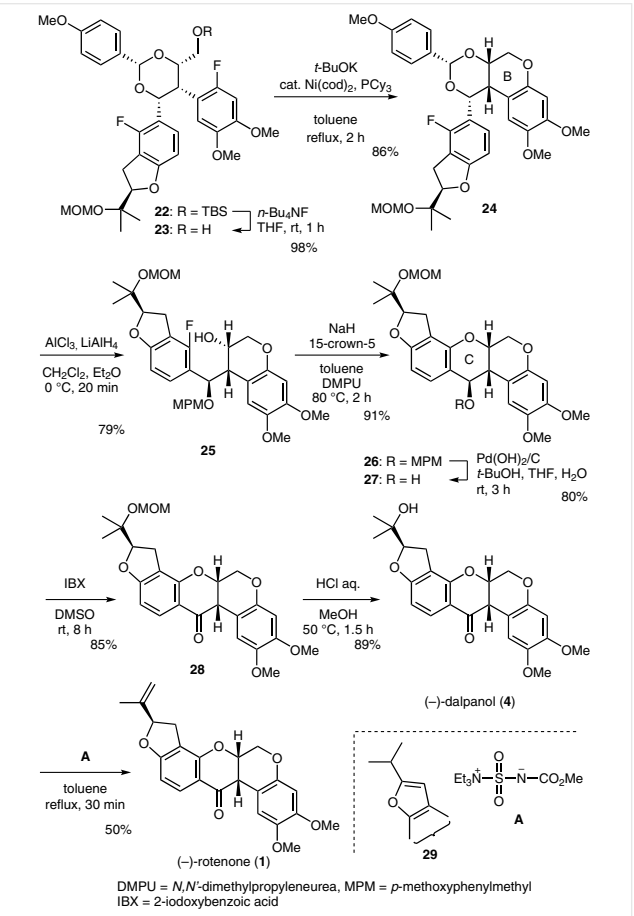
Next, the DE-ring unit **6** was lithiated (*s*-BuLi, Et_2O, TMEDA, –78 °C, 1 h), and allowed to react with ketone **19** to give epoxy alcohol **20** in 89% yield (Scheme 12). As expected, epoxy alcohol **20** was obtained as a single diastereomer, which proved to be epimeric to **9**.[14] Pleasingly, the reaction of epoxy alcohol **20** with $BF_3{\cdot}OEt_2$ (20 mol%, CH_2Cl_2, 0 °C, 15 min), followed by the reaction with $NaBH_4$ 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.[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**).



Scheme 12 Key 1,2-rearrangement

Acetal **22** was converted into the pentacyclic rotenoid skeleton via two S_NAr oxy-cyclizations (Scheme 13). Upon treatment of **22** with *n*-Bu_4NF (THF, rt, 1 h), the TBS group was removed, giving alcohol **23** in 98% yield, ready for the S_NAr 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 PCy_3 (30 mol%) (toluene, reflux, 2 h), giving tetrahydropyran **24** in 86% yield. Upon treatment with AlH_3,[31] anisylidene acetal **24** was regioselectively cleaved, giving alcohol **25** as a single isomer (79% yield). The S_NAr oxy-cyclization of **25** proceeded smoothly (NaH, 15-crown-5, toluene,

DMPU, 80 °C), giving pentacycle **26** in 91% yield. The MPM protecting group in **26** was detached by hydrogenation [H_2, $Pd(OH)_2$/C, THF, *t*-BuOH, H_2O, rt, 3 h] to give alcohol **27** in 80% yield, which was oxidized with 2-iodobenzoic acid (DMSO, rt, 5 h) to give ketone **28** in 85% yield. Removal of the MOM group in **28** (aq HCl, MeOH, 50 °C, 1.5 h) gave (–)-dalpanol (**4**) in 89% yield. Recrystallization from benzene gave **4** as colorless needles {mp 199–200 °C, $[\alpha]_D^{22}$ –1.1 × 10^2 (*c* 0.52, $CHCl_3$) [Lit.[32a] mp 196 °C, $[\alpha]_D^{22}$ –136.3 (*c* 0.62, $CHCl_3$)]}. All the physical data of the synthetic sample of **4** (^{1}H and ^{13}C NMR, IR, HRMS) coincided with the reported data.[32]



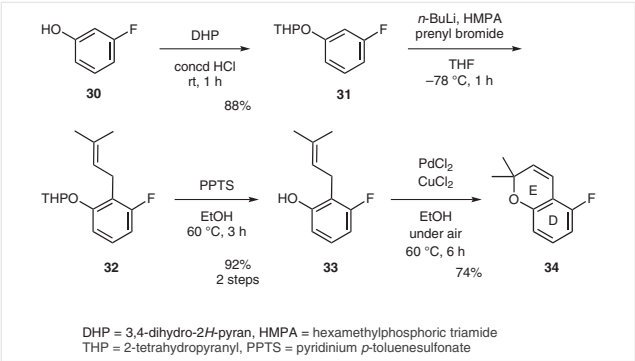
Scheme 13 Endgame to rotenone (**1**)

Finally, treatment of **4** with Burgess reagent[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, $[\alpha]_D^{23}$ –1.5 × 10^2 (*c* 0.070, $CHCl_3$) [Lit.[11] mp 165–166 °C, $[\alpha]_D^{23}$ –177 (*c* 2, $CHCl_3$)]}. All the physical data of the synthetic sample of **1** coincided with the reported data.[11,34] Direct comparison was done with an authentic sample (^{1}H and ^{13}C NMR, IR, HRMS).[35]

2.4 Total Synthesis of (–)-Deguelin (2)

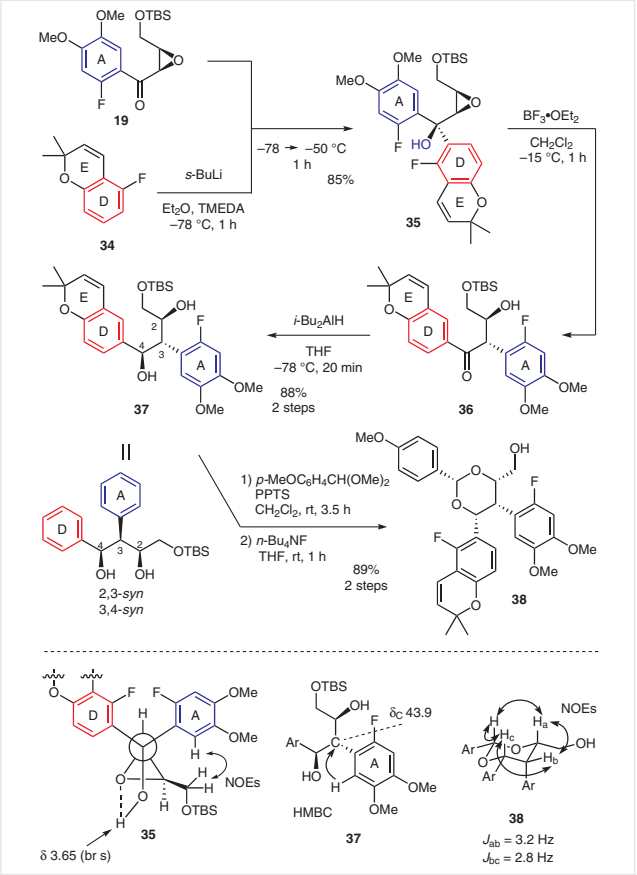
Since deguelin (**2**) is one of the rotenoids that is attracting recent interest by its anticancer activity,[7a] we decided to apply the above-stated synthetic route to the synthesis of **2**, as described in this section.

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).[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 $PdCl_2$ and $CuCl_2$ under air[37] gave the DE-ring unit **34** in 74% yield.



Scheme 14 DE-Ring building block for the synthesis of deguelin

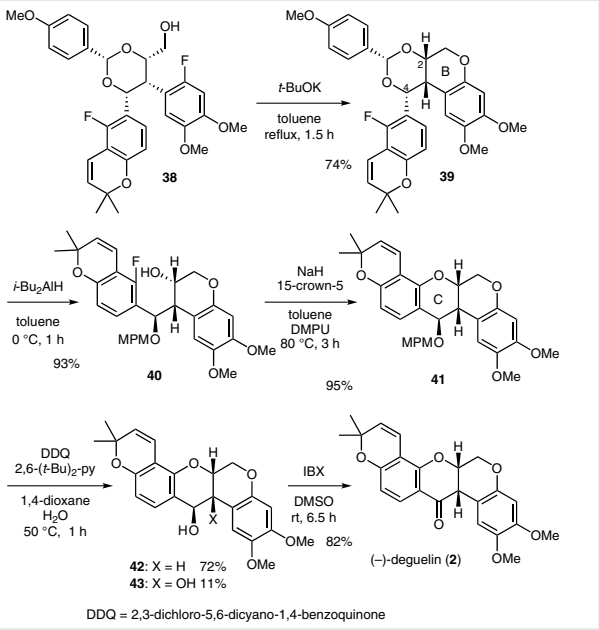
Scheme 15 illustrates the synthesis of epoxy alcohol **35** for the projected 1,2-shift. *ortho*-Lithiation of **34** with *s*-BuLi (Et_2O, TMEDA, –78 °C, 1 h) followed by reaction with ketone **19** gave epoxy alcohol **35** in 85% yield as a single diastereomer. The stereostructure of **35** was assigned as shown based on ^{1}H NMR and NOE analyses. The projected 1,2-rearrangement of epoxy alcohol **35** was achieved by treatment with $BF_3{\cdot}OEt_2$ (20 mol%, CH_2Cl_2, –15 °C, 40 min). The crude material containing aldol **36** was immediately reduced with *i*-Bu_2AlH, 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_2AlH reduction.



Scheme 15 Synthesis of diol **37** via 1,2-shift and reduction

Having acetal **38** as an advanced intermediate, the next stages were the formations of the B- and C-pyran rings by dual S_NAr oxy-cyclizations (Scheme 16). The S_NAr reaction of **38** proceeded smoothly by the action of *t*-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_2AlH 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.[38] Note that AlH_3 was used for this purpose in the synthesis of **1** (see **24** → **25**, Scheme 13). *i*-Bu_2AlH turned out to be superior for this transformation. The second S_NAr 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_2O (8:1), 50 °C, 1 h] gave alcohol **42** in 72% yield. We noted that small



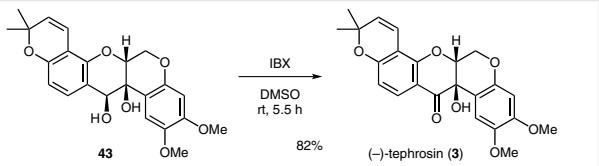
Scheme 16 Endgame in the synthesis of **2**

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 (^1H, ^{13}C NMR, IR, high-resolution MS) of the synthetic material **2** coincided with those of the reported data:[40] $[\alpha]_D^{20}$ –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[7b] 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 (^1H, ^{13}C NMR, IR, high-resolution MS) of the synthetic material **3** matched with the reported data:[40b,c] $[\alpha]_D^{20}$ –98 (*c* 0.20, $CHCl_3$) {Lit.[40c] $[\alpha]_D^{20}$ –86 (*c* 0.2, $CHCl_3$)}.



Scheme 17 Conversion of **43** into (–)-**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 $K_2Cr_2O_7$ for converting (–)-**2**, obtained from natural rotenone (–)-**1**, while Xu[10e] 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** [$K_2Cr_2O_7$, AcOH, H_2O (3:1), 60 °C, 0.5 h), which cleanly gave (–)-**3** in 94% yield {$[\alpha]_D^{20}$ –84 (*c* 0.23, $CHCl_3$)} (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].

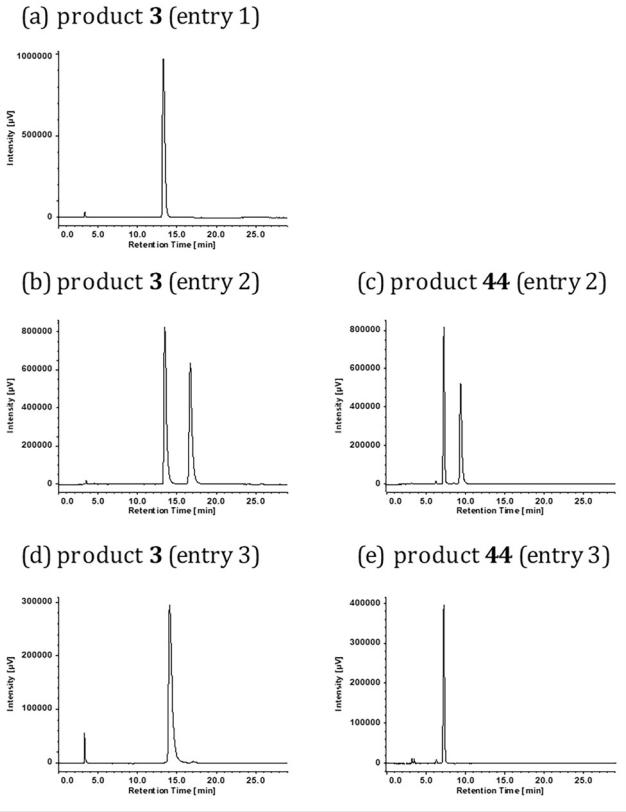
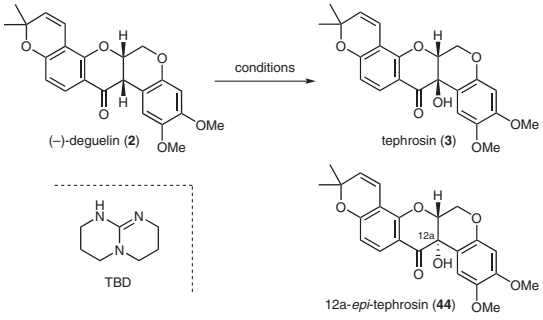


Figure 4 Assessment of *ee* for **3** and **44**. Conditions for **3**: CHIRALPAK® IB (ϕ 4.6 mm × 250 mm), hexane/EtOAc (4:1); for **44**: CHIRALPAK® IF (ϕ 4.6 mm × 250 mm), hexane/EtOAc (3:2); flow rate: 1.0 mL/min, 25 °C, 254 nm.

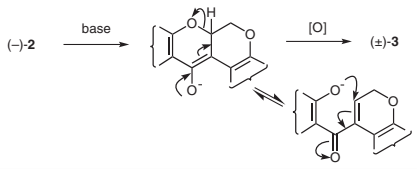
In contrast, the result was markedly different with the Xu protocol (Table 1, entry 2). Upon exposure of (–)-**2** to O_2 (1 atm) in the presence of Cu_2O and TBD (DMSO, rt, 4.5 h), a separable mixture of two products formed. After separation by preparative TLC (hexane/EtOAc 1:1), the less polar product (R_f = 0.65) was the desired product **3** (53% yield), while

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



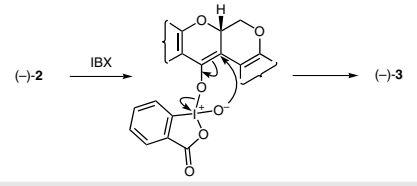
Entry	Conditions	Results
1	$K_2Cr_2O_7$, AcOH, 60 °C	**3**: 94% (>99% *ee*)
2	O_2, Cu_2O, TBD, DMSO, rt	**3**: 53% (~0% *ee*), **44**: 27% (~0% *ee*)
3	IBX, DMSO, 60 → 80 °C	**3**: 44% (>99% *ee*), **44**: 44% (>99% *ee*)

the more polar one (R_f = 0.51) was the epimer **44** (27% yield),[42] 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 enantiopure, [(d) and (e) in Figure 4]. This result could be explained by an intramolecular oxygen transfer (Equation 6), albeit with no diastereofacial selectivity.



Equation 6 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_NAr 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_2Cl_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. ^{1}H, ^{13}C, and ^{19}F NMR were measured on a Bruker Avance III (600 MHz) spectrometer. 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 recorded on Thermo Scientific Nicolet iS5 FTIR spectrometer. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded by using Thermo Scientific Nicolet iS5 FTIR spectrophotometer equipped iD5 ATR accessory. Optical rotations ($[\alpha]_D$) were measured on a Jasco P-3000 polarimeter. High-resolution mass spectra (HRMS) were obtained with Bruker Daltonics micrOTOF-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_2Cl_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% $Na_2S_2O_3$. The crude products were extracted with CH_2Cl_2 (3 ×), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (140 °C (oven temp)/7.4 mmHg) to afford bromobenzene **8** (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}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.848 (s, 3 H), 3.853 (s, 3 H), 6.70 (d, $J_{C,F}$ = 9.8 Hz, 1 H), 6.96 (d, $J_{C,F}$ = 6.5 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 56.3, 56.6, 97.5 (d, $J_{C,F}$ = 22.5 Hz), 100.8 (d, $J_{C,F}$ = 27.7 Hz), 115.1, 145.9, (d, $J_{C,F}$ = 2.8 Hz), 149.2 (d, $J_{C,F}$ = 8.3 Hz), 153.5 (d, $J_{C,F}$ = 239.4 Hz).

^{19}F NMR (565 MHz, $CDCl_3$): δ = –118.6.

Anal. Calcd for $C_8H_8BrFO_4$: C, 40.88; H, 3.43. Found: C, 40.73; H, 3.41.

diol 14

To a solution of D-araboascrobic acid (35.2 g, 0.200 mol) in deionized H_2O (500 mL) was added Na_2CO_3 (42.4 g, 0,400 mol) and H_2O_2 (34.5%, 40 mL, 0.41 mol) at 0 °C over 10 min. After stirring for 30 min at 40 °C, activated charcoal (Norit A®, 8.0 g) was added. The mixture was stirred for 30 min at the same temperature, and for 5 min at 80 °C. The reaction mixture was filtered through a Celite pad, washed with deionized H_2O (100 mL), and aq 6 M HCl (150 mL) was added to the filtrate. After concentration in vacuo, the residue was dissolved in EtOAc, and heated to reflux. The hot mixture was decanted (5 ×) and the supernatant liquid was cooled to rt. The resulting precipitate was collected by filtration to afford diol **14** (9.00 g, 38%) as colorless needles. The mother liquor was concentrated in vacuo, and the residue was purified by recrystallization from EtOAc (3 ×) to afford diol **14** (13.2 g, 56%; total yield: 94%) as colorless needles; R_f = 0.29 ($CHCl_3$/MeOH 5:1); mp 94–96 °C (EtOAc); $[\alpha]_D^{20}$ –73 (*c* 1.00, H_2O).

IR (ATR): 3544, 3278, 1744, 1464, 1432, 1229, 1184, 1150, 1027, 953, 771 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 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): δ = 68.4, 69.5, 71.8, 176.4.

Anal. Calcd for $C_4H_6O_4$: C, 40.68; H, 5.12. Found: C, 40.81; H, 5.00.

Tosylate 15

To a solution of diol **14** (4.00 g, 33.9 mmol) in pyridine (16 mL) was added TsCl (7.10 g, 37.2 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_2SO_4), and concentrated in vacuo. The residue was purified by trituration with CH_2Cl_2 (3 ×) to afford tosylate **15** (6.95 g, 76%) as a white solid; R_f = 0.70 ($CHCl_3$/MeOH 5:1); mp 183–184 °C (EtOAc); $[\alpha]_D^{20}$ –45 (*c* 1.01, acetone).

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

^{1}H 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).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.8, 68.1, 71.2, 74.3, 128.4, 130.2, 131.6, 146.3, 168.5.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{12}O_6SNa$ $[M + Na]^+$: 295.02468; found: 295.0249.

lactone 16

To a solution of tosylate **15** (4.03 g, 14.8 mmol) in MeCN (70 mL) was added K_2CO_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); $[\alpha]_D^{20}$ +28 (*c* 1.04, $CHCl_3$).

IR (neat): 3094, 2971, 1782, 1386, 1365, 1046, 953, 852, 783 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.81 (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).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 49.6, 55.0, 68.3, 170.7.

Anal. Calcd for $C_4H_6O_4$: C, 48.01; 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 Et_2O (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 Et_2O (60 mL) was added to the mixture, which was stirred for 1 h at –78 °C. 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 dissolved in DMF (60 mL), to which *tert*-butyldimethylsilyl 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 Et_2O (3 ×), and the combined organic extracts were washed with H_2O (2 ×) and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by trituration with Et_2O (4 ×) to afford epoxy ketone **19** (3.72 g, 83%) as a white solid. The mother liquor was concentrated in vacuo, and the residue was purified by flash column chromatography (SiO_2, hexane/EtOAc 4:1) to afford **19** (475 mg, 11%; total yield: 94%) as a white solid; mp 98–99 °C (Et_2O); R_f = 0.56 (hexane/EtOAc 3:1); $[\alpha]_D^{20}$ +70 (*c* 1.15, $CHCl_3$).

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

^1H NMR (600 MHz, $CDCl_3$): δ = –0.09 (s, 3 H), –0.02 (s, 3 H), 0.78 (s, 9 H), 3.56–3.59 (m, 2 H), 3.77–3.80 (m, 1 H), 3.91 (s, 3 H), 3.95 (s, 3 H), 4.26 (dd, *J* = 5.7 Hz, $J_{H,F}$ = 4.5 Hz, 1 H), 6.64 (d, $J_{H,F}$ = 11.9 Hz, 1 H), 7.40 (d, $J_{H,F}$ = 6.5 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.6, –5.3, 18.3, 25.8, 56.6, 56.7, 58.5 (d, $J_{C,F}$ = 1.8 Hz, 1 C), 59.5 (d, $J_{C,F}$ = 12.0 Hz, 1 C), 60.7, 99.9 (d, $J_{C,F}$ = 30.0 Hz, 1 C), 110.4 (d, $J_{C,F}$ = 4.8 Hz, 1 C), 115.5 (d, $J_{C,F}$ = 14.9 Hz, 1 C), 146.0, 155.3 (d, $J_{C,F}$ = 10.8 Hz, 1 C), 158.9 (d, $J_{C,F}$ = 251.1 Hz, 1 C), 189.8 (d, $J_{C,F}$ = 5.1 Hz, 1 C).

^{19}F NMR (565 MHz, $CDCl_3$): δ = –115.1.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{27}FO_5SiNa$ $[M + Na]^+$: 393.1504; found: 393.1562.

Alcohol 23

To a solution of acetal **22** (235 mg, 0.322 mmol) in THF (1.8 mL) was added *n*-Bu_4NF (1.0 M in THF, 0.95 mL, 0.96 mmol) at rt. 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 (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 2:1 to 1:1) to afford alcohol **23** (194 mg, 98%) as a white amorphous solid.

Alcohol 27

To a solution of ether **26** (20.1 mg, 0.0346 mmol) in *t*-BuOH (0.85 mL), THF (0.85 mL), and H_2O (0.17 mL) was added ASCA-2 type Pd/C [10% $Pd(OH)_2$/C, 17.5 mg] and stirred under H_2 atmosphere at rt for 3 h. After changing the atmosphere from H_2 to argon, the reaction mixture was filtered through a Celite pad (washed with CH_2Cl_2) and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to afford alcohol **27** (21.9 mg, 80%) as a white amorphous solid.

Ketone 28

To a solution of alcohol **27** (7.6 mg, 0.017 mmol) in DMSO was added IBX (5.3 mg, 0.019 mmol) at rt. After stirring for 4 h, the reaction mixture was reacted with IBX in two portions (first: 7.8 mg, 0.028 mmol; second: 9.8 mg, 1 h). After stirring for 1 h, the reaction was quenched by the addition of sat. aq $NaHCO_3$. 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 1:1) to afford ketone **28** (6.4 mg, 85%) as a white amorphous solid; R_f = 0.50 (hexane/EtOAc 1:1); $[\alpha]_D^{22}$ –122 (*c* 0.980, $CHCl_3$).

IR (neat): 2917, 1673, 1609, 1513, 1456, 1348, 1309, 1197, 1091, 1040 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): 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 (dd, *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).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.5, 22.7, 27.5, 44.6, 55.3, 55.9, 56.3, 62.3, 72.2, 76.9, 90.9, 91.4, 100.9, 104.8, 104.9, 110.4, 113.2, 113.4, 129.8, 143.9, 147.4, 149.5, 157.9, 167.5, 189.0.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{28}O_8$ $[M + H]^+$: 457.18569; found: 457.18602.

(–)-Dalpanol (4)

To a solution of ketone **28** (17.8 mg 0.0390 mmol) in MeOH (1.5 mL) was added aq 1 M HCl (0.39 mL) at rt. After stirring for 1.5 h at 50 °C, the reaction was quenched by adding sat. aq $NaHCO_3$. The 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 (–)-dalpanol (**4**; 14.3 mg, 89%) as a pale yellow solid. All physical data are fully identical with those of the reported data.[14]

fluorobenzene 31

To a mixture of 3-fluorophenol (**30**; 6.2 mL, 68 mmol) and 3,4-dihydro-2*H*-pyran (9.2 mL, 0.10 mol) was added concd HCl (0.1 mL) at –35 °C. After warming to rt over 1 h, the reaction was stopped by adding sat. aq $NaHCO_3$. The 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 recrystallized from hexane to afford fluorobenzene **31** (11.7 g, 88%) as colorless crystals; mp 49–50 °C (hexane); R_f = 0.55 (hexane/EtOAc 9:1).

IR (neat): 2945, 2875, 1611, 1593, 1488, 1261, 1138, 1038, 975 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.57–1.64 (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), 5.40 (dd, *J* = 3.3, 3.3 Hz, 1 H), 6.68 (ddd, *J* = 8.3, 8.3 Hz, $J_{H,F}$ = 2.2 Hz, 1 H), 6.79 (d, $J_{H,F}$ = 10.9 Hz, 1 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 7.21 (dd, *J* = 8.3 Hz, $J_{H,F}$ =11.7 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 18.7, 25.1, 30.2, 62.0, 96.5, 104.2 (d, $J_{C,F}$ = 24.0 Hz, 1 C), 108.3 (d, $J_{C,F}$ = 21.0 Hz, 1 C), 112.1 (d, $J_{C,F}$ = 3.0 Hz, 1 C), 130.0 (d, $J_{C,F}$ = 9.0 Hz, 1 C), 158.4 (d, $J_{C,F}$ = 12.0 Hz, 1 C), 163.5 (d, $J_{C,F}$ = 243 Hz, 1 C).

^{19}F NMR (565 MHz, $CDCl_3$): δ = –115.0.

Anal. Calcd for $C_{11}H_{13}FO_4$: C, 67.33; H, 6.68. Found: C, 67.47; H, 6.62.

phenol 33

To a solution of fluorobenzene **31** (105 mg, 0.535 mmol) in THF (1 mL) was added *n*-BuLi (1.64 M in hexane, 0.40 mL, 0.66 mmol) at –78 °C. After stirring for 1 h at –78 °C, hexamethylphosphoric triamide (0.36 mL) in THF (1 mL) and prenyl bromide (111 mg, 0.745 mmol) in THF (1 mL) were added. After stirring for 1 h at –78 °C, the reaction was stopped by adding H_2O. The crude products were ex-

tracted with Et_2O (3 ×), and the combined organic extracts were washed with H_2O (2 ×) and brine, dried (Na_2SO_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_2SO_4), and concentrated in vacuo. The residue was purified 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): 3434, 2969, 2916, 1619, 1599, 1467, 1285, 1165, 1032, 782 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.74 (s, 3 H), 1.80 (s, 3 H), 3.39 (d, J = 7.2 Hz, 2 H), 5.25 (t, J = 7.2 Hz, 1 H), 5.37 (s, 1 H, OH), 6.59 (d, J = 8.1 Hz, 1 H), 6.63 (dd, J = 8.8 Hz, $J_{H,F}$ = 8.9 Hz, 1 H), 7.03 (ddd, J = 8.8, 8.1 Hz, $J_{H,F}$ = 7.4 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.8 22.0 (d, $J_{C,F}$ = 4.5 Hz, 1 C), 25.8, 107.6 (d, $J_{C,F}$ = 23.2 Hz, 1 C), 111.4 (d, $J_{C,F}$ = 3.0 Hz, 1 C), 114.8 (d, $J_{C,F}$ = 18.8 Hz, 1 C), 120.9, 127.3 (d, $J_{C,F}$ = 10.5 Hz, 1 C), 135.2, 155.7 (d, $J_{C,F}$ = 7.4 Hz, 1 C), 161.3 (d, $J_{C,F}$ = 243.7 Hz, 1 C).

^{19}F NMR (565 MHz, $CDCl_3$): δ = –120.4.

HRMS (ESI): m/z calcd for $C_{11}H_{12}FO$ [M – H]$^-$: 179.08777; found: 179.08734.

ether 34

To a solution of phenol **33** (302mg, 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_2O) 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_2SO_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}.

^1H NMR (600 MHz, $CDCl_3$): δ = 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, $J_{H,F}$ = 7.2 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.9, 76.4, 107.3 (d, $J_{C,F}$ = 21.0 Hz, 1 C), 110.0 (d, $J_{C,F}$ = 18.2 Hz, 1 C), 112.1 (d, $J_{C,F}$ = 3.1 Hz, 1 C), 115.1 (d, $J_{C,F}$ = 4.7 Hz, 1 C), 128.9 (d, $J_{C,F}$ = 10.3 Hz, 1 C), 130.7 (d, $J_{C,F}$ = 2.5 Hz, 1 C), 154.0 (d, $J_{C,F}$ = 7.0 Hz, 1 C), 158.6 (d, $J_{C,F}$ = 248.1 Hz, 1 C).

^{19}F NMR (565 MHz, $CDCl_3$): δ = –126.5.

HRMS (APCI): m/z calcd for $C_{11}H_{10}FO$ [M – H]$^-$: 179.07212; found: 179.07276.

Epoxy Alcohol 35

To a solution of ether **34** (83.1 mg, 0.466 mmol) in Et_2O (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 azeotropically dried (toluene, 1 mL 3 ×) epoxy ketone **19** (103 mg, 0.278 mmol) in Et_2O (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_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 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); $[\alpha]_D^{20}$ +24 (c 0.990, $CHCl_3$).

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

^1H NMR (600 MHz, $CDCl_3$): 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 (d, $J_{H,F}$ = 1.5 Hz, 1 H, OH), 3.80 (dd, 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, $J_{H,F}$ = 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, $J_{H,F}$ = 12.0 Hz, 1 H) 6.78 (dd, J = 8.6 Hz, $J_{H,F}$ = 8.6 Hz, 1 H), 7.12 (d, $J_{H,F}$ = 7.0 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.3, –5.1, 18.4, 26.0, 28.0, 28.2, 56.3, 56.5, 59.6, 61.1, 61.8 (d, $J_{C,F}$ = 7.5 Hz, 1 C), 71.9 (d, $J_{C,F}$ = 3.9 Hz, 1 C), 76.8, 100.2 (d, $J_{C,F}$ = 28.7 Hz, 1 C), 109.8 (d, $J_{C,F}$ = 6.0 Hz, 1 C), 110.7 (d, $J_{C,F}$ = 19.0 Hz, 1 C), 111.4 (d, $J_{C,F}$ = 2.9 Hz, 1 C), 115.1 (d, $J_{C,F}$ = 6.1 Hz, 1 C), 120.4 (d, $J_{C,F}$ = 15.0 Hz, 1 C), 124.8 (d, $J_{C,F}$ = 12.0 Hz, 1 C), 127.3 (d, $J_{C,F}$ = 4.5 Hz, 1 C),131.1, 145.3 (d, $J_{C,F}$ = 2.2 Hz, 1 C), 149.4 (d, $J_{C,F}$ = 10.5 Hz, 1 C), 153.2 (d, $J_{C,F}$ = 232.5 Hz, 1 C), 154.0, 156.4 (d, $J_{C,F}$ = 250.5 Hz, 1 C).

^{19}F NMR (565 MHz, $CDCl_3$): δ = –125.7, –121.2.

HRMS (ESI): m/z calcd for $C_{29}H_{39}F_2O_6Si$ [M + H]$^+$: 549.24785; found: 549.24903.

Diol 37

To a solution of epoxy alcohol **35** (2.09 g, 3.81 mmol) in CH_2Cl_2 (70 mL) was added $BF_3{\cdot}OEt_2$ (126 mg, 0.888 mmol) in CH_2Cl_2 (6.2 mL) at –15 °C. After stirring for 40 min, the reaction was stopped by adding sat. aq $NaHCO_3$. The crude product was extracted with CH_2Cl_2 (3 ×), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in THF (76 mL), to which *i*-Bu_2AlH (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 ×). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc 1:2) to afford diol **37** (1.85 g, 88%) as a white amorphous solid; R_f = 0.42 (hexane/EtOAc 2:1); $[\alpha]_D^{20}$ +111 (c 1.60, $CHCl_3$).

IR (neat): 3476, 2930, 2857, 1624, 1577, 1513, 1465, 1448, 1257, 1116 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): 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 (dd, 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 (dd, J = 5.7 Hz, $J_{H,F}$ = 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, $J_{H,F}$ = 11.1 Hz, 1 H), 6.57 (d, J = 10.0 Hz, 1 H), 6.89 (dd, J = 8.4 Hz, $J_{H,F}$ =8.4 Hz, 1 H), 7.33 (d, $J_{H,F}$ = 6.7 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.4, –5.3, 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, $J_{C,F}$ = 30.0 Hz, 1 C), 109.6 (d, $J_{C,F}$ = 18.8 Hz, 1 C), 112.0 (d, $J_{C,F}$ = 2.8 Hz, 1 C), 113.7 (d, $J_{C,F}$ = 4.9 Hz, 1 C), 114.3 (d, $J_{C,F}$ = 15.0 Hz, 1 C), 115.4 (d, $J_{C,F}$ = 5.7 Hz, 1 C), 121.0 (d, $J_{C,F}$ = 13.5 Hz, 1 C), 127.6 (d, $J_{C,F}$ = 6.1 Hz, 1 C), 130.8 (d, $J_{C,F}$ = 2.1 Hz, 1 C), 144.9 (d, $J_{C,F}$ = 2.5 Hz, 1 C), 148.6 (d, $J_{C,F}$ = 10.0 Hz, 1 C), 153.2 (d, $J_{C,F}$ = 6.9 Hz, 1 C), 155.5 (d, $J_{C,F}$ = 248.4 Hz, 1 C), 156.1 (d, $J_{C,F}$ = 237.5 Hz, 1 C).

^{19}F NMR (565 MHz, $CDCl_3$): δ = –132.1, –131.4.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{41}F_2O_6Si$ [M + H]$^+$: 551.26350; found: 551.26466.

Alcohol 38

To a solution of diol **37** (1.96 g, 3.56 mmol) in CH_2Cl_2 (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 $NaHCO_3$. The crude product was were extracted with CH_2Cl_2 (3 ×), and the combined organic extracts were washed with brine, dried (Na_2SO_4), 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 (assessed by ^{1}H NMR analysis). The mixture was dissolved in THF (18 mL), to which *n*-Bu_4NF (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 (Na_2SO_4), 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; R_f = 0.55 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ +156 (*c* 1.89, $CHCl_3$).

IR (neat): 2935, 2916, 2849, 1616, 1514, 1465, 1251, 1209, 1092, 1036, 1009, 827 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.38 (s, 3 H), 1.89 (br s, 1 H, OH), 3.44–3.53 (m, 2 H), 3.55 (dd, *J* = 3.0, 2.9 Hz, 1 H), 3.75 (s, 3 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 4.55 (ddd, *J* = 7.7, 4.2, 2.9 Hz, 1 H), 5.53 (d, *J* = 3.0 Hz, 1 H), 5.62 (d, *J* = 9.9 Hz, 1 H), 5.93 (s, 1 H), 6.28 (d, *J* = 8.3 Hz, 1 H), 6.34 (d, $J_{H,F}$ = 11.2 Hz, 1 H), 6.55 (d, *J* = 9.9 Hz, 1 H), 6.73 (dd, *J* = 8.3 Hz, $J_{H,F}$ = 8.3 Hz, 1 H), 6.95 (d, *J* = 8.7 Hz, 2 H), 7.59 (d, *J* = 8.7 Hz, 2 H), 7.61 (d, $J_{H,F}$ = 6.9 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.4, 27.8, 35.6 (d, $J_{C,F}$ = 2.1 Hz, 1 C), 55.3, 55.8, 56.3, 64.1, 76.2, 76.3, 80.8, 98.8 (d, $J_{C,F}$ = 30.0 Hz, 1 C), 102.0, 109.2 (d, $J_{C,F}$ = 18.3 Hz, 1 C), 111.5 (d, $J_{C,F}$ = 2.8 Hz, 1 C), 113.5 (d, $J_{C,F}$ = 14.8 Hz, 1 C), 113.7, 113.8 (d, $J_{C,F}$ = 4.7 Hz, 1 C), 115.2 (d, $J_{C,F}$ = 5.4 Hz, 1 C), 118.1 (d, $J_{C,F}$ = 13.1 Hz, 1 C), 126.9 (d, $J_{C,F}$ = 5.9 Hz, 1 C), 127.5, 130.6, 130.7 (d, $J_{C,F}$ = 2.1 Hz, 1 C), 144.4 (d, $J_{C,F}$ = 2.4 Hz, 1 C), 148.2 (d, $J_{C,F}$ = 10.1 Hz, 1 C), 152.8 (d, $J_{C,F}$ = 6.7 Hz, 1 C), 154.5 (d, $J_{C,F}$ = 248.3 Hz, 1 C), 155.6 (d, $J_{C,F}$ = 237.5 Hz 1 C), 160.2.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –132.3, –129.0.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{32}F_2O_7Na$ [M + Na]$^+$: 577.20083; found: 577.20079.

Ether 39

To a solution of azeotropically 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 NH_4Cl. The crude product was 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 ether **39** (20.3 mg, 74%) as a colorless oil; R_f = 0.77 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ +44 (*c* 0.815, $CHCl_3$).

IR (neat): 2974, 2834, 1619, 1515, 1480, 1463, 1345, 1249, 1216, 1199, 1158, 1113, 1045, 835 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.46 (s, 3 H), 3.31 (s, 3 H), 3.41–3.43 (m, 1 H), 3.777 (s, 3 H), 3.781 (s, 3 H), 4.04 (d, *J* = 10.7 Hz, 1 H), 4.41–4.54 (m, 2 H), 5.50 (d, *J* = 2.6 Hz, 1 H), 5.71 (d, *J* = 9.9 Hz, 1 H), 5.86 (s, 1 H), 5.95 (s, 1 H), 6.42 (s, 1 H), 6.62 (d, *J* = 9.9 Hz, 1 H), 6.63 (d, *J* = 8.9 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.27 (dd, *J* = 8.9 Hz, $J_{H,F}$ = 8.9 Hz, 1 H, overlapped with $CHCl_3$ signal), 7.38 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.5, 27.9, 35.5 (d, $J_{C,F}$ = 2.1 Hz, 1 C), 55.2, 55.3, 55.7, 68.2, 72.0, 76.3, 76.5, 100.9, 101.8, 109.7 (d, $J_{C,F}$ = 17.7 Hz, 1 C), 110.1, 111.5, 112.3 (d, $J_{C,F}$ = 2.7 Hz, 1 C), 113.6, 114.8 (d, $J_{C,F}$ = 5.4 Hz, 1 C), 119.8 (d, $J_{C,F}$ = 12.8 Hz, 1 C), 127.8 (d, $J_{C,F}$ = 6.1 Hz, 1 C), 127.8, 130.7, 131.4 (d, $J_{C,F}$ = 2.1 Hz, 1 C), 142.2, 148.1, 149.2, 153.6 (d, $J_{C,F}$ = 6.6 Hz, 1 C), 154.5 (d, $J_{C,F}$ = 248.1 Hz, 1 C), 160.1.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –131.5.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{31}FO_7Na$ [M + Na]$^+$: 557.19460; found: 557.19289.

Alcohol 40

To a solution of azeotropically dried (toluene, 1 mL, 3 ×) ether **39** (189 mg, 0.354 mmol) in toluene (7.1 mL) was added *i*-Bu_2AlH (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 (Na_2SO_4), 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; R_f = 0.55 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ +26 (*c* 1.26, $CHCl_3$).

IR (neat): 3484, 2930, 1617, 1512, 1464, 1214, 1197, 1116, 1045, 822 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.46 (s, 3 H), 1.47 (s, 3 H), 1.96 (d, *J* = 7.7 Hz, 1 H), 3.35 (dd, *J* = 7.6, 4.1 Hz, 1 H), 3.57 (s, 3 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 3.82–3.84 (m, 1 H), 3.97 (d, *J* = 10.5 Hz, 1 H), 4.15 (dd, *J* = 10.5, 7.7 Hz, 1 H), 4.31 (d, *J* = 11.1 Hz, 1 H), 4.40 (d, *J* = 11.1 Hz, 1 H), 5.02 (d, *J* = 7.6 Hz, 1 H), 5.68 (d, *J* = 10.0 Hz, 1 H), 6.40 (s, 1 H), 6.61 (d, *J* = 10.0 Hz, 1 H), 6.64 (d, *J* = 8.4 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 1 H), 7.11 (s, 1 H), 7.16 (dd, *J* = 8.4 Hz, $J_{H,F}$ = 8.4 Hz, 1 H), 7.21 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.9, 28.1, 44.2, 55.3, 55.8, 56.0, 65.4, 69.4, 70.2, 76.7, 77.0 100.2, 109.7 (d, $J_{C,F}$ = 18.8 Hz, 1 C), 112.0, 112.3 (d, $J_{C,F}$ = 2.8 Hz, 1 C), 113.1, 113.8, 115.1 (d, $J_{C,F}$ = 5.2 Hz, 1 C), 118.6 (d, $J_{C,F}$ = 13.7 Hz, 1 C), 128.8 (d, $J_{C,F}$ = 6.1 Hz, 1 C), 129.4, 130.1, 130.8 (d, $J_{C,F}$ = 2.1 Hz, 1 C), 143.2, 147.9, 148.7, 153.7 (d, $J_{C,F}$ = 6.8 Hz, 1 C), 156.6 (d, $J_{C,F}$ = 249.5 Hz, 1 C), 159.2; the missing signal was overlapped with $CDCl_3$ signals.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –130.4.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{33}FO_7Na$ [M + Na]$^+$: 559.21025; found: 559.20992.

Ether 41

To a solution of azeotropically dried (toluene, 1 mL, 3 ×) alcohol **40** (604 mg, 1.13 mmol) in toluene (50.6 mL) and DMPU (5.6 mL) were added 15-crown-5 ether (221 µL, 1.12 mmol) and NaH (82.2 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 NH_4Cl. The crude product was extracted with Et_2O (3 ×), and the combined organic extracts were washed with H_2O (3 ×) and brine, dried (Na_2SO_4), 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; R_f = 0.67 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ +6.3 (*c* 0.865, $CHCl_3$); $[\alpha]_{436}^{20}$ +17 (*c* 1.52, $CHCl_3$).

IR (neat): 2931, 1610, 1512, 1458, 1248, 1195, 1146, 1116, 1091, 1033 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.38 (s, 3 H), 3.47 (dd, *J* = 3.0, 2.8 Hz, 1 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 4.21 (d, *J* = 11.7 Hz, 1 H), 4.57 (d, *J* = 11.2 Hz, 1 H), 4.58–4.60 (m, 1 H), 4.61 (d, *J* = 11.2 Hz, 1 H), 4.73 (d, *J* = 3.0 Hz, 1 H), 4.83 (dd, *J* = 3.2, 2.8 Hz, 1 H), 5.49 (d, *J* = 10.0 Hz, 1 H), 6.30 (d, *J* = 8.3 Hz, 1 H), 6.36 (s, 1 H), 6.49 (s, 1 H), 6.66 (d, *J* = 10.0 Hz, 1 H), 6.86 (d, *J* = 8.3 Hz, 1 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.7, 28.2, 35.7, 55.3, 55.7, 56.8, 66.2, 67.6, 69.7, 72.4, 76.0, 100.9, 108.5, 108.8, 109.7, 110.4, 110.7, 113.9, 116.7, 128.5, 129.4, 130.4, 130.6, 143.4, 148.5, 149.0, 149.8, 154.2, 159.3.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{32}O_7Na$ [M + Na]$^+$: 539.20402; found: 539.20992; *m*/*z* calcd for $C_{31}H_{33}O_7$ [M + H]$^+$: 517.22208; found: 517.22191.

Alcohol 42 and Diol 43

To a solution of ether **41** (18.0 mg, 0.0348 mmol) and 2,6-di-*tert*-butylpyridine (40.2 mg, 0.210 mmol) in 1,4-dioxane (1.6 mL) and H_2O (0.2 mL) was added DDQ (24.2 mg, 0.107 mmol) at rt. After stirring for 1 h at 50 °C, the reaction was stopped by adding aq 10% $Na_2S_2O_3$ and sat. aq $NaHCO_3$. The crude materials 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 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_f = 0.47 (hexane/EtOAc 2:3); $[\alpha]_D^{20}$ –51 (*c* 0.560, $CHCl_3$).

IR (neat): 3461, 2973, 2930, 1511, 1462, 1221, 1194, 1146, 1090, 1016 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.39 (s, 3 H), 1.97 (d, *J* = 3.2 Hz, 1 H, OH), 3.33 (dd, *J* = 3.3, 3.1 Hz, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.23 (d, *J* = 11.6 Hz, 1 H), 4.57 (dd, *J* = 11.6, 3.7 Hz, 1 H), 4.78 (dd, *J* = 3.7, 3.1 Hz, 1 H), 5.06, (d, *J* = 3.3, 3.2 Hz, 1 H), 5.52 (d, *J* = 10.0 Hz, 1 H), 6.35 (d, *J* = 8.3 Hz, 1 H), 6.39 (s, 1 H), 6.64 (s, 1 H), 6.65 (d, *J* = 10.0 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.8, 28.1, 37.7, 55.8, 56.7, 66.0, 66.6, 67.3, 76.1, 101.0, 108.9, 109.4, 109.7, 110.4, 113.6, 116.5, 128.8, 129.3, 143.4, 148.2, 149.1, 149.3, 154.3.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{25}O_6$ [M + H]$^+$: 397.16456; found: 397.16451.

43

R_f = 0.39 (hexane/EtOAc 1:2); $[\alpha]_D^{20}$ –106 (*c* 0.515, $CHCl_3$).

IR (neat): 3420, 2929, 1510, 1464, 1263, 1198, 1153, 1115, 1033, 755 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.37 (s, 3 H), 2.46 (d, *J* = 3.4 Hz, 1 H, OH), 3.38 (s, 1 H, OH), 3.78 (s, 3 H), 3.78 (s, 3 H), 4.39–4.42 (m, 1 H), 4.51 (d, *J* = 11.8 Hz, 1 H), 4.54 (dd, *J* = 11.8, 2.7 Hz, 1 H), 5.03 (d, *J* = 3.4 Hz, 1 H), 5.51 (d, *J* = 10.0 Hz, 1 H), 6.33 (d, *J* = 8.3 Hz, 1 H), 6.39 (s, 1 H), 6.61 (d, *J* = 10.0 Hz, 1 H), 6.76 (s, 1 H) 6.97 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.8, 28.1, 55.8, 56.7, 64.5, 64.9, 68.6, 70.0, 76.2, 101.0, 108.9, 109.6, 109.6, 109.9, 113.3, 116.4, 128.9, 129.9, 143.8, 148.7, 149.4, 150.9, 154.7.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{25}O_7$ [M + H]$^+$: 413.15948; found: 413.16034.

(–)-Deguelin (2)

To a solution of alcohol **42** (10.0 mg, 0.0251 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 sat. aq $NaHCO_3$ and aq 10% $Na_2S_2O_3$. The crude product was 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 (–)-deguelin (**2**; 8.1 mg, 82%) as a yellow amorphous solid; R_f = 0.63 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ –46 (*c* 0.20, $CHCl_3$).

IR (neat): 2966, 2926, 1673, 1597, 1579, 1513, 1442, 1345, 1274, 1214, 1198, 1112, 1094 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.45 (s, 3 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 3.84 (d, *J* = 4.1 Hz, 1 H), 4.19 (d, *J* = 12.0 Hz, 1 H), 4.64 (dd, *J* = 12.1, 3.1 Hz, 1 H), 4.92 (dd, *J* = 4.1, 3.1 Hz, 1 H), 5.56 (d, *J* = 10.1 Hz, 1 H), 6.45 (d, *J* = 8.7 Hz, 1 H), 6.45 (s, 1 H), 6.65 (d, *J* = 10.1 Hz, 1 H), 6.79 (s, 1 H), 7.75 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): 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.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}O_6$ [M + H]$^+$: 395.14891; found: 395.14955.

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 sat. aq $NaHCO_3$ and aq 10% $Na_2S_2O_3$. The crude product was 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**; 14.5 mg, 82%) as a white amorphous solid; R_f = 0.65 (hexane/ EtOAc 1:1); $[\alpha]_D^{20}$ –98 (*c* 0.20, $CHCl_3$).

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

^{1}H NMR (600 MHz, $CDCl_3$): 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* = 10.1 Hz, 1 H), 7.73 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.3, 28.5, 55.9, 56.4, 63.9, 67.4, 76.3, 78.0, 101.1, 108.6, 109.1, 109.4, 111.1, 111.9, 115.4, 128.6, 128.8, 144.0, 148.4, 151.1, 156.7, 160.8, 191.4.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}O_7Na$ [M + Na]$^+$: 433.12577; found: 433.12717.

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

To a solution of (–)-deguelin (**2**; 5.4 mg, 0.014 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 $NaHCO_3$ and aq 10% $Na_2S_2O_3$. 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 1:1) to afford (–)-tephrosin (**3**; 2.4 mg, 44%) as a white amorphous solid and (+)-12a-*epi*-tephrosin (**44**; 2.4 mg, 44%) as a white solid.

(–)-Tephrosin (3)

$[\alpha]_D^{20}$ –81 (*c* 0.18, $CHCl_3$).

(+)-12a-*epi*-Tephrosin (44)

Mp 208–210 °C; R_f = 0.51 (hexane/EtOAc 1:1); $[\alpha]_D^{23}$ +2.6 × 10^2 (*c* 0.10, $CHCl_3$).

IR (neat) 3450, 1690, 1594, 1575, 1504, 1447, 1266, 1109, 1088 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.45 (s, 3 H), 1.49 (s, 3 H), 2.75 (s, 1 H, OH), 3.85 (s, 3 H), 3.92 (s, 3 H), 4.41 (dd, *J* = 9.8, 4.4 Hz, 1 H), 4.50 (dd, *J* = 11.5, 9.8 Hz, 1 H), 4.66 (dd, *J* = 11.5, 4.4 Hz, 1 H), 5.63 (d, *J* = 10.1 Hz, 1 H), 6.43 (s, 1 H), 6.57 (d, *J* = 8.7 Hz, 1 H), 6.65 (d, *J* = 10.1 Hz, 1 H), 7.80 (d, *J* = 8.7 Hz, 1 H), 7.84 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.1, 28.5, 55.9, 56.4, 61.7, 66.1, 77.8, 100.4, 109.0, 109.7, 112.2, 112.6, 113.6, 115.4, 129.3, 129.6, 143.8, 149.5, 151.1, 155.7, 159.7, 187.4; the missing signal was overlapped with $CDCl_3$ signals.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}O_6$ $[M - H_2O + H]^+$: 393.13326; found: 393.13374.

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 Cu_2O (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 aq 10% $Na_2S_2O_3$. The crude products was 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; $[\alpha]_D^{20}$ –84 (*c* 0.23, $CHCl_3$).

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Supporting Information

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