Natural Products

International Edition: DOI: 10.1002/anie.201609253
German Edition: DOI: 10.1002/ange.201609253

Stereocontrolled Total Syntheses of (−)-Rotenone and (−)-Dalpanol by 1,2-Rearrangement and S_NAr Oxycyclizations

Kayo Nakamura, Ken Ohmori, and Keisuke Suzuki**

In memory of Sankichi Takei

Abstract: *The total syntheses of (−)-rotenone and (−)-dalpanol have been achieved by a group-selective, stereospecific 1,2-shift of an epoxy alcohol and S_NAr cyclizations. Three oxacycles are constructed, thus illustrating a versatile synthetic route to various rotenoids.*

Rotenoids constitute a class of isoflavonoids isolated from various leguminous species. The generic name came from rotenone (**1**),[1] a historical natural product isolated as a poisonous ingredient from *Derris* and *Lonchocarpus* plants, traditionally used as a fish poison and insecticide (Figure 1).[2] The structure of **1** was determined in 1932 by three independent groups,[3] and synthetic endeavors culminated in the total syntheses, in racemic form, by Matsui in 1960,[4] and in chiral, non-racemic form, by Yamashita in 1979.[5] After a hiatus, synthetic interest has recently resurged because of the discovery of novel bioactivities in rotenoids,[6] including (−)-**1** as well as (−)-dalpanol [(−)**2**][7a,b] and (−)-deguelin [(−)-**3**].[7c,8]

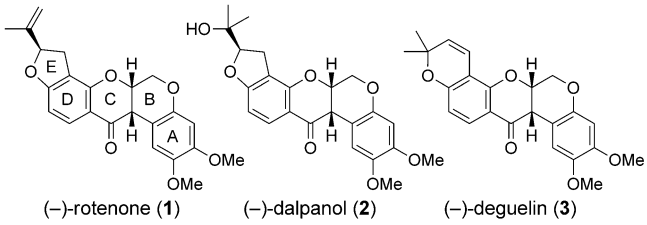
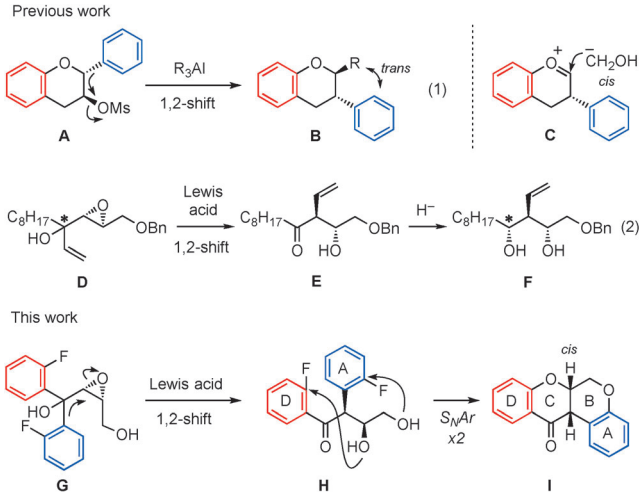


Figure 1. Natural rotenoids.

Herein, we describe the stereocontrolled total syntheses of (−)-**1** and (−)-**2** by the selective 1,2-rearrangement of an epoxy alcohol derivative and a threefold S_NAr oxycyclization. Scheme 1 shows how our synthetic plan has evolved, starting with our recent synthetic access to isoflavonoids (Scheme 1 a),[9] which was inspired by the biosynthetic flavonoid→isoflavonoid isomerization, including a 1,2-shift.[10] Activation of the catechin-derived mesylate **A** with an organoaluminum reagent effects stereospecific 1,2-shift of an aryl group, and stereoselective delivery of an aluminum ligand (R) gives the *trans*-product **B**.[9] This strategy, however, was not suitable for rotenoid synthesis (**C**), as a synthetic equivalent to an umpoled synthon ($^-CH_2OH$) is required and must be installed from a *cis* direction.



Scheme 1. Synthetic planning of rotenoids.

To settle these issues, an idea surfaced from our previous study of the 1,2-rearrangement-based strategy in natural product synthesis.[11] The reaction in Scheme 1 b exemplifies stereospecific conversion of the *trans*-epoxy alcohol **D** into the *anti*-aldol **E** (vice versa, *cis*→*syn*, not shown).[12] Importantly, although **D** is a diastereomeric mixture at the stereogenic center marked with an asterisk, exclusive 1,2-migration of the vinyl group occurs, while the octyl group remains intact, thus reflecting a large difference in their migratory aptitudes (vinyl ⩾ octyl). The conformational flexibility allows both diastereomers of **D** to adopt their respective reactive conformers, thus placing the vinyl group antiperiplanar to the epoxide C–O bond to be cleaved upon Lewis-acid activation to manifest a typical Curtin–Hammett system.[13] In addition, subsequent reduction of **E** allows control of three contiguous chiral centers in **F**,[11c] which also turned out to be relevant to the present project as discussed below.

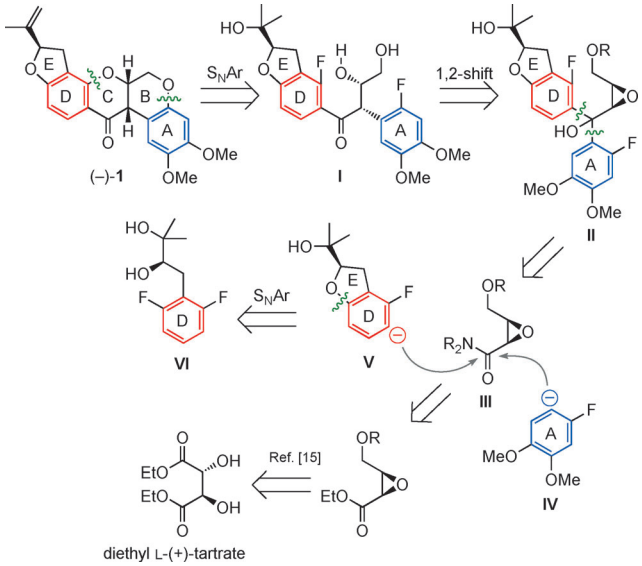
We envisioned a plan for the synthesis of rotenoids starting from the *cis*-epoxy alcohol **G** which already has a hydroxymethyl (CH_2OH) group installed (Scheme 1). Assuming stereospecificity, the 1,2-shift of a fluorophenyl group in **G** would give the *syn*-aldol **H**, possessing a structural feature ideally suited for constructing two tetrahydropyran

[*] Dr. K. Nakamura, Prof. Dr. K. Ohmori, Prof. Dr. K. Suzuki
Department of Chemistry, Tokyo Institute of Technology
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551 (Japan)
E-mail: kohmori@chem.titech.ac.jp
ksuzuki@chem.titech.ac.jp

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201609253.

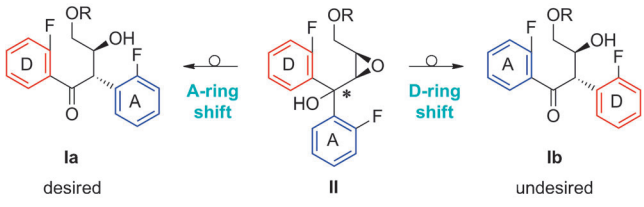
rings by dual S_NAr oxycyclizations to give the tetracycle **I**. In the synthesis of catechin-class polyphenols,[14] we had many successes with such S_NAr cyclizations, which proved viable for aryl fluorides without the aid of electron-withdrawing group(s), such as the nitro. The key challenge was how to discriminate between two similar aryl groups: the scenario was that the blue one undergoes 1,2-shift to become the A ring, while the red one the D ring, and not vice versa.

Scheme 2 shows the retrosynthesis of (−)-**1**. Assuming the B- and C-pyran rings would be constructed by the S_NAr oxycyclizations,[14] the diol **I**, having two fluorophenyl units corresponding to the A and D rings, was chosen as the precursor. The aldol **I** could be traced back to the epoxy alcohol **II**, assuming the 1,2-rearrangement.[11] The key intermediate **II** would be assembled from the chiral, non-racemic epoxy amide **III**, derived from diethyl L-(+)-tartrate,[15] to which the A-ring unit **IV**[16] and the DE-ring unit **V** would be added. The furan ring (E-ring) in **V** would also be cyclized by the S_NAr reaction of the diol **VI**.



Scheme 2. Retrosynthesis of (−)-**1**.

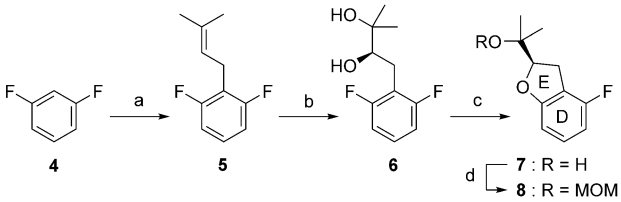
A critical question of this plan was the group selectivity in the 1,2-rearrangement, $\mathbf{II_a}\rightarrow\mathbf{I_a}$ (Scheme 3). The desired product $\mathbf{I_a}$ is obtained by the 1,2-shift of the A ring (blue), whereas the competing shift of the D ring (red) gives the isomeric product $\mathbf{I_b}$. As discussed previously, we had many examples to show that such group selectivity is dictated by the difference



Scheme 3. Two competing 1,2-shifts.

in the migratory aptitude (MA),[11] where the stereochemistry at the migrating origin (asterisked) is not consequential. In the present case, however, both aryl groups share a similar substitution pattern including an *o*-fluoro group, and thus, their intrinsic MAs also appeared to be similar. Accordingly, we had a premise that the conformational effect would play an important role, and the identity of the tertiary alcohol center, marked with an asterisk, would influence the reaction course, although to an unknown extent.

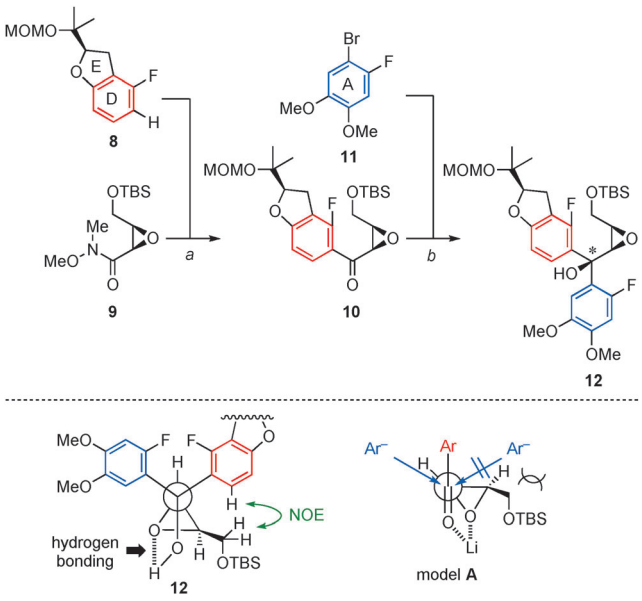
With these points in mind, our study began with the preparation of the benzofuran **8**, the DE-ring unit (Scheme 4). Regioselective lithiation of 1,3-difluorobenzene (**4**)[17] followed by the addition of prenyl bromide gave the isoprene **5** in 94% yield. The asymmetric Sharpless dihydroxylation, using $(DHQD)_2PHAL$ as the ligand,[18] gave the (*R*)-diol **6** in 97% enantiomeric excess (97% yield).[19] The next stage was the first S_NAr oxycyclization: Upon treatment of **6** with NaH, cyclization to the five-membered ring, rather than the six-membered ring, proceeded smoothly to give the benzofuran **7** in quantitative yield. The tertiary alcohol in **7** was protected with a MOM group, giving **8** in 93% yield.



Scheme 4. Synthesis of the DE-ring fragment **8**. Reagents and conditions: a) *n*BuLi (1 equiv), HMPA (1 equiv), THF, −78 °C, 1 h; $Me_2C{=}CHCH_2Br$ (1.1 equiv), −78 °C→RT, 2 h (94%). b) $(DHQD)_2PHAL$ (2 mol%), $K_2OsO_2(OH)_4$ (1 mol%), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (2 equiv), *t*BuOH, H_2O, 0 °C, 120 h (97%, 97% *ee*). c) NaH (3 equiv), DMF, RT, 5 h (quant.). d) MOMCl (10 equiv), iPr_2NEt (20 equiv), nBu_4NI (20 mol%), CH_2Cl_2, RT, 24 h (93%). $(DHQD)_2PHAL$ = 1,4-bis-dihydroquinidine phthalazine, DMF = dimethylformamide, HMPA = hexamethyl-phosphoric triamide, MOM = methoxymethyl, THF = tetrahydrofuran.

With **8** in hand, we set out to prepare substrates for the 1,2-rearrangement (Scheme 5). We arbitrarily installed the DE ring first, followed by the A ring, which led us to several interesting findings. The fluorobenzene **8** was lithiated and combined with the chiral, non-racemic epoxy amide **9**,[20] thus giving epoxy ketone **10** in 72% yield. The bromide **11**[16] was subjected to bromine–lithium exchange and combined with the ketone **10**. The stereoselectivity at this stage was greater than expected, thus giving the epoxy alcohol **12** (84% yield) as a single product, whose stereochemistry was assigned as shown by ^1H NMR analysis. The NOE correlation was diagnostic, thanks to the restricted conformation resulting from the presence of hydrogen bonding.[21] The chelation model **A** accounts for the stereochemical course of the addition, where the access of the nucleophile from the right side is blocked by the *cis*-substituent, thus leading to exceptionally high selectivity.[22]

The stage was set to examine the key 1,2-rearrangement of the epoxy alcohol **12** (Scheme 6). Upon treatment with



Scheme 5. Synthesis of the epoxy alcohol **12**. Reagents and conditions: a) **8** (2 equiv), *s*BuLi (2 equiv), Et_2O, TMEDA (9:1), −78 °C, 1 h; **9** (1 equiv), −78 °C, 30 min (72 %). b) **11** (1 equiv), *n*BuLi (1 equiv), Et_2O, −78 °C, 1 h; **10** (1 equiv), −78 → −30 °C, 1 h (84 %). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

$BF_3{\cdot}OEt_2$, **12** was consumed within 20 minutes (TLC analysis). Since the aldol product **13** proved labile, as it decomposed and/or epimerized, so the crude material was reduced with $NaBH_4$ to give the diol **14** as a single product (50 % yield). Importantly, extensive NMR studies proved that **14** resulted from the 1,2-shift of the DE-ring unit (red), which was unfortunately the wrong group selectivity.

Of additional importance, the above-stated process gave us a hint for establishing the requisite stereochemical triad in a single step. The stereochemistry of the three contiguous chiral centers in **14** was assigned. By careful analysis of the anisylidene acetal **15**, derived from **14**, it was proven that: 1) the 1,2-shift occurred stereospecifically with inversion, and 2) the reduction of the aldol product was stereoselective, as rationalized by model **B** (Scheme 6).[11c,23]

Even though we obtained the undesired isomer, the perfect group selectivity gave us significant insight. Figure 2 shows two hydrogen-bonded conformers of **12**, where the conformer **12b** is disfavored by steric hindrance posed by the *cis*-substituent R (= CH_2OTBS). The conformer **12a** would be highly populated, a hypothesis which was supported by calculation on a simple model substrate (R = CH_3, and aryls = C_6H_5), showing an energy difference as large as 5.4 kcal mol^{-1}.

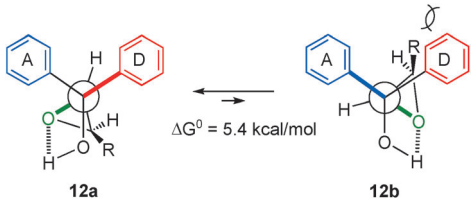
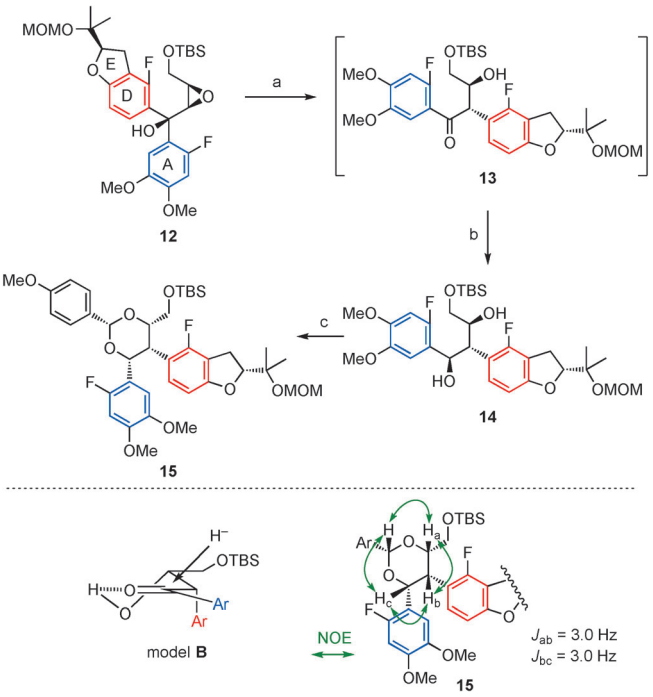


Figure 2. Rationale for the group selectivity.

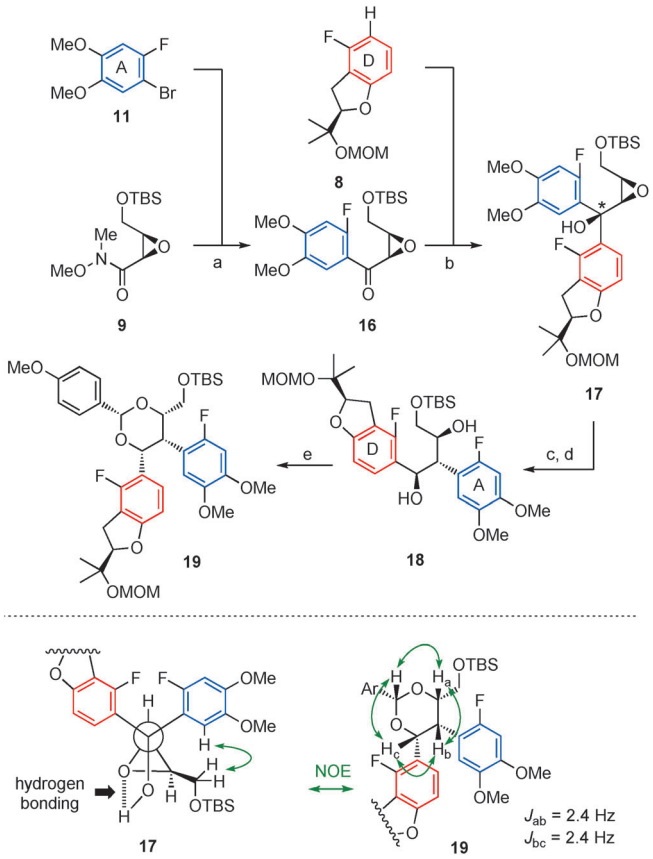


Scheme 6. 1,2-Shift-reduction sequence. Reagents and conditions: a) $BF_3{\cdot}OEt_2$ (20 mol %), CH_2Cl_2, 0 °C, 20 min. b) $NaBH_4$, MeOH, RT, 30 min (50 %, 2 steps). c) *p*-$MeOC_6H_4CH(OMe)_2$ (3 equiv), PPTS (30 mol %), CH_2Cl_2, RT, 3 h (51 %). PPTS = pyridinium *para*-toluenesulfonate.

Assuming **12a** 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) which is cleaved upon Lewis-acid activation.[24] 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 100/0 in this case, is reflected in the product distribution.[25]

This insight clearly guided us to change the order of installing the A- and D-ring units in the preparation of the substrate (Scheme 7). A bromine–lithium exchange reaction of **11**, followed by treatment with **9** gave the epoxy ketone **16** in 90 % yield. The DE-ring unit **8** was lithiated as before, and was reacted with **16** to give the epoxy alcohol **17** in 89 % yield as a single diastereomer. As expected, the stereochemistry of **17** proved to be epimeric to that of **12** by the NOE study. Pleasingly, the key step proceeded perfectly: the reaction of **17** with $BF_3{\cdot}OEt_2$, followed by the reaction with $NaBH_4$, gave the diol **18** as a single isomer in 71 % yield. Extensive NMR studies ascertained that **18** was derived from the migration of the A ring (blue). Further conversion of **18** into **19** (single diastereomer, 89 % yield) allowed the stereochemical assignment by ^1H NMR analysis.

To complete the synthesis, the acetal **19** was converted into the pentacyclic rotenoid skeleton by two S_NAr oxycyclizations (Scheme 8). Upon treatment of **19** with nBu_4NF, the TBS group was removed to give the alcohol **20** in 92 % yield, thus making it ready for the S_NAr reaction. The initial attempt using a combination of KH and 18-crown-6 gave the

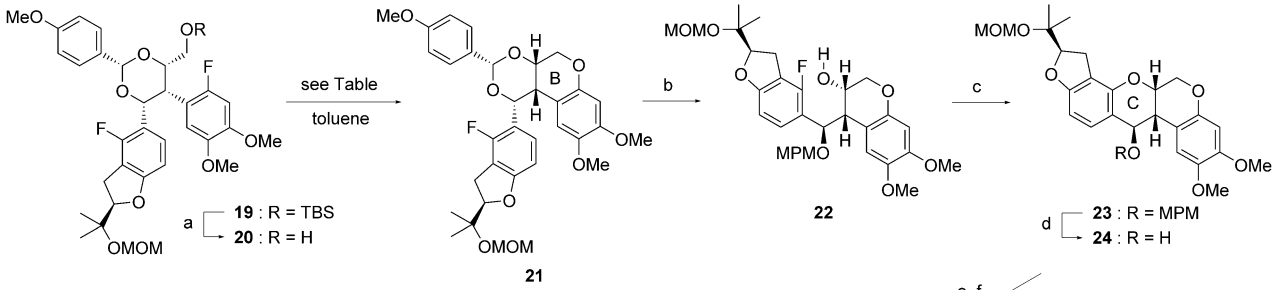


Scheme 7. Isomeric-series conversions. Reagents and conditions: a) **11** (1 equiv), *n*BuLi (1 equiv), Et_2O, −78 °C, 1 h; **10** (1 equiv), −78 °C, 1 h (90%). b) **8** (2 equiv), *s*BuLi (2 equiv), Et_2O, TMEDA (9:1), −78 °C, 1 h; **16** (1 equiv), −78→−30 °C, 1.5 h (89%). c) $BF_3{\cdot}OEt_2$ (20 mol%), CH_2Cl_2, 0 °C, 15 min. d) $NaBH_4$, MeOH, RT (71%, 2 steps). e) *p*-$MeOC_6H_4CH(OMe)_2$ (3 equiv), PPTS (20 mol%), CH_2Cl_2, RT, 4 h (89%).

desired product **21** in 46% yield (run 1 in Table). The low material balance was due to the competing benzylic deprotonation, thus inducing cleavage of the THF ring (**C**). Use of a milder base, *t*BuOK, led to poor conversion with recovery of a sizable amount of **20** (run 2). However, we were pleased to find that the S_NAr reaction was nicely facilitated by the addition of a catalytic amount of a nickel species,[26] giving the desired tetrahydropyran **21** in 86% yield (run 3). This catalytic effect in the C–O bond formation will also be useful in the broader context of organic synthesis.[27]

Treatment of **21** with AlH_3[28] allowed regioselective reductive cleavage of the anisylidene acetal, giving the alcohol **22** as a single isomer (79% yield). The last S_NAr oxy-cyclization of **22** proceeded smoothly under simple basic conditions (NaH, 15-crown-5, toluene, DMPU, 80 °C) to give the pentacycle **23** in 91% yield. The MPM group in **23** was removed by hydrogenation to give the alcohol **24** in 64% yield. Dess–Martin oxidation of **24** followed by removal of the MOM group gave (−)-dalpanol [(−)-**2**] as colorless needles in good yield {mp 199–200 °C (benzene), $[\alpha]_D^{20}=-1.1\times10^2$ ($c=0.52$, $CHCl_3$), [*lit.* 196 °C, $[\alpha]_D^{20}=-136.3$ ($c=0.62$, $CHCl_3$)]}.[7a] All the physical data of the synthetic sample of (−)-**2** (^1H and ^{13}C NMR, IR, high-resolution MS) coincided with the reported data.[7a,b,29]

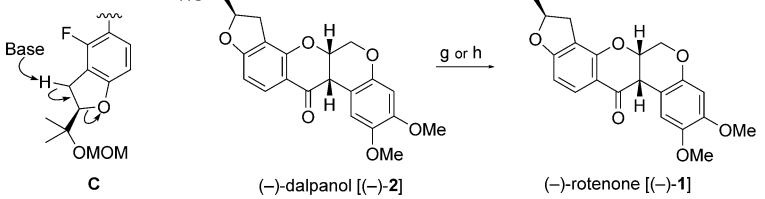
Finally, the conversion of (−)-**2** into (−)-rotenone [(−)-**1**] was examined. Treatment of (−)-**2** with $SOCl_2$ gave a mixture of *exo*/*endo* olefins, from which (−)-rotenone [(−)-**1**] was isolated in 40% yield.[30] By contrast, Burgess' reagent[31] selectively gave (−)-**1** in 50% yield. In this case, an unexpected side product, the benzofuran derivative, was obtained in 13% yield (see the Supporting Information), presumably arising from a cation generated at the tertiary carbon center followed by a 1,2-hydride shift. Recrystallization afforded (−)-**1** as colorless crystals {mp 153–154 °C



Table

run	base	additive	temperature	yield of **21**
1	KH	18-crown-6 DMPU	80 °C	46% (8%)[a]
2	*t*BuOK	–	reflux	12% (52%)[a]
3	*t*BuOK	$Ni(cod)_2$[b] PCy_3[c]	reflux	86%

[a] Recovery of **20** [b] 10 mol% [c] 30 mol%.



Scheme 8. Endgame. Reagents and conditions: a) nBu_4NF (3 equiv), THF, RT, 1 h (92%). b) $AlCl_3$ (3 equiv), $LiAlH_4$ (2 equiv), CH_2Cl_2, Et_2O, 0 °C, 20 min (79%). c) NaH (3 equiv), 15-crown-5 (2 equiv), toluene, DMPU (9:1), 80 °C, 2 h (91%). d) H_2, 10% Pd/C (10 mol%), *t*BuOH, H_2O, RT, 15 h (64%). e) Dess–Martin periodinane (2 equiv), CH_2Cl_2, RT, 15 min. f) HCl aq., MeOH, 50 °C, 1.5 h (52–60%, 2 steps). g) $SOCl_2$, pyridine, 0 °C, 15 min (40%). h) Burgess' reagent, toluene, reflux, 30 min (50%). Burgess' reagent = methyl *N*-(triethylammoniumsulphonyl)carbamate, DMPU = *N*,*N*′-dimethylpropyleneurea.

(benzene), $[\alpha]_D^{23}=-1.5\times10^2$ ($c=0.070$, $CHCl_3$), [*lit.* 165–166 °C, $[\alpha]_D^{23}=-177$ ($c=2$, $CHCl_3$)]}.[5] All the physical data of the synthetic sample of (−)-**1** (^{1}H and ^{13}C NMR, IR, high-resolution MS) also coincided with the reported data[5,32] and the synthetic material was identical to that of an authentic sample by direct comparison.[33]

In conclusion, an effective synthetic approach to rotenoids has been developed, and will be useful for the synthesis of other congeners. Further studies are in progress in our laboratory.

Acknowledgements

This work was supported by Grant-in-Aid for Specially Promoted Research (No. 23000006, 16H06351, 16H01137 and 16H04107) from JSPS. We thank Mr. Seiya Matsuoka for experimental assistance.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclizations · heterocycles · natural products · rearrangements · total synthesis

[1] E. Geoffroy, *Ann. Inst. Colon. Marseilles* **1896**, *2*, 1.
[2] a) F. B. La Forge, H. L. Haller, L. E. Smith, *Chem. Rev.* **1933**, *7*, 181–213; b) D. Barton, K. Nakanishi, *Comprehensive Natural Products Chemistry*, *Vol. 8*, Elsevier, Amsterdam, **1999**, pp. 340–343; c) P. M. Dewick, *Medicinal Natural Products A Biosynthetic Approach Second Edition*, Wiley, Hoboken, **2001**, pp. 154–157.
[3] a) A. Butenandt, W. McCartney, *Justus Liebigs Ann. Chem.* **1932**, *494*, 17–41; b) F. B. LaForge, H. L. Haller, *J. Am. Chem. Soc.* **1932**, *54*, 810–818; c) S. Takei, S. Miyajima, M. Ohno, *Ber. Dtsch. Chem.* **1932**, *65*, 1041–1049.
[4] M. Miyano, A. Kobatashi, M. Matsui, *Bull. Agric. Chem. Soc. Jpn.* **1960**, *24*, 540–542.
[5] I. Sasaki, K. Yamashita, *Agric. Biol. Chem.* **1979**, *43*, 137–139.
[6] a) R. Betarbet, T. B. Sherer, G. Mackenzie, M. Garcia-Osuna, A. V. Panov, J. T. Greenamyre, *Nat. Neurosci.* **2000**, *3*, 1301–1306; b) P. Caboni, T. B. Sherer, N. Zhang, G. Taylor, H. M. Na, J. T. Greenamyre, J. E. Casida, *Chem. Res. Toxicol.* **2004**, *17*, 1540–1548.
[7] a) D. Adinarayana, M. Radhakrushniah, J. Rajasekhara, R. Campbell, L. Crombie, *J. Chem. Soc. C* **1971**, 29–32; b) N. Nakatani, M. Matsui, *Agric. Biol. Chem.* **1997**, *41*, 601–602; c) E. P. Clark, *J. Am. Chem. Soc.* **1931**, *53*, 313–317.
[8] For recent syntheses of **3**, see: a) J. Garcia, S. Barluenga, K. Beebe, L. Neckers, N. Winssinger, *Chem. Eur. J.* **2010**, *16*, 9767–9771; b) R. L. Farmer, K. A. Scheidt, *Chem. Sci.* **2013**, *4*, 3304–3309; c) S. Lee, H. An, D.-J. Chang, J. Jang, K. Kim, J. Sim, J. Lee, Y.-G. Suh, *Chem. Commun.* **2015**, *51*, 9026–9029.
[9] K. Nakamura, K. Ohmori, K. Suzuki, *Chem. Commun.* **2015**, *51*, 7012–7014.
[10] M. F. Hashim, T. Hakamatsuka, Y. Ebizuka, U. Sankawa, *FEBS Lett.* **1990**, *271*, 219–222.
[11] a) K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki, G. Tsuchihashi, *J. Am. Chem. Soc.* **1986**, *108*, 3827–3829; b) K. Suzuki, T. Matsumoto, K. Tomooka, K. Matsumoto, G. Tsuchihashi, *Chem. Lett.* **1987**, *16*, 113–116; c) K. Suzuki, M. Miyazawa, M. Shimazaki, G. Tsuchihashi, *Tetrahedron* **1988**, *44*, 4061–4072; d) T. Nagasawa, K. Taya, M. Kitamura, K. Suzuki, *J. Am. Chem. Soc.* **1996**, *118*, 8949–8950, and references therein.
[12] If a TMS group was present on the vinyl group, the reduction stereoselectivity was reversed, and was exploited in the stereodivergent syntheses of avenaciolide and isoavenaciolide (see Ref [11c]).
[13] For Curtin–Hammett principle, see J. I. Seeman, *Chem. Rev.* **1983**, *83*, 83–134.
[14] a) K. Ohmori, T. Yano, K. Suzuki, *Org. Biomol. Chem.* **2010**, *8*, 2693–2696; b) S. Stadlbauer, K. Ohmori, F. Hattori, K. Suzuki, *Chem. Commun.* **2012**, *48*, 8425–8427; c) T. Yano, K. Ohmori, H. Takahashi, T. Kusumi, K. Suzuki, *Org. Biomol. Chem.* **2012**, *10*, 7685–7688; d) Y. Ito, K. Ohmori, K. Suzuki, *Angew. Chem. Int. Ed.* **2014**, *53*, 10129–10133; *Angew. Chem.* **2014**, *126*, 10293–10297, and references therein.
[15] a) S. Saito, Y. Nagano, M. Miyazaki, M. Inaba, T. Moriwake, *Tetrahedron Lett.* **1986**, *27*, 5249–5252; b) S. Saito, T. Ishikawa, A. Kuroda, K. Koga, T. Moriwake, *Tetrahedron* **1992**, *48*, 4067–4086.
[16] J. M. Harris, B. R. Neustadt, J. Hao, A. W. Stamford, WO2009111449, **2009**.
[17] F. Mongin, R. Maggi, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 2771–2777.
[18] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768–2771; see also, H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
[19] The enantiomeric purity of **6** was assessed by HPLC analysis with a chiral stationary phase. See the Supporting Information.
[20] The epoxy amide **9** was prepared from the corresponding epoxy ester (see Ref. [15]), by hydrolysis (KOH, EtOH, 90% yield) and subsequent direct condensation of the resulting potassium salt with Me(MeO)NH·HCl using EDCI (77%). For this amide formation protocol, see: L. Yu, A. Kokai, A. K. Yudin, *J. Org. Chem.* **2007**, *72*, 1737–1741.
[21] Presence of a hydrogen bond was suggested by a downfield shift of the ^{1}H NMR signal of the hydroxy proton ($\delta=3.60$, $CDCl_3$).
[22] For pertinent references for chelation-controlled addition to epoxy carbonyl compounds, see: a) T. Oishi, T. Nakata, *Acc. Chem. Res.* **1984**, *17*, 338–344; b) S. Okamoto, T. Yoshino, H. Tsujiyama, F. Sato, *Tetrahedron Lett.* **1991**, *32*, 5793–5796; c) M. Adachi, K. Higuchi, N. Thasana, H. Yamada, T. Nishikawa, *Org. Lett.* **2012**, *14*, 114–117, and references therein.
[23] Reductions of *syn*-aldols are often stereoselective, giving an all-*syn*-isomer, as rationalized by assuming that the hydrogen-bonded aldol substrates undergo the hydride attack, where two factors, that is, the steric and the chelation effects, are cooperative.
[24] For examples of the group selectivity of migration in the pinacol rearrangements, see: a) P. I. Pollak, D. Y. Curtin, *J. Am. Chem. Soc.* **1950**, *72*, 961–965; b) C. J. Collins, *J. Am. Chem. Soc.* **1955**, *77*, 5517–5523; c) B. M. Benjamin, H. J. Schaeffer, C. J. Collins, *J. Am. Chem. Soc.* **1957**, *79*, 6160–6164; d) K. Suzuki, K. Tomooka, M. Shimazaki, G. Tsuchihashi, *Tetrahedron Lett.* **1985**, *26*, 4781–4784.
[25] For an account on the early contributions,[24a,b] see: R. T. Morrison, R. N. Boyd, *Organic Chemistry*, 3rd ed., Allyn & Bacon, Boston, **1981**, pp. 898–904.
[26] For selected examples of the nickel catalysis for activation of aryl fluorides, see: a) Y. Kiso, K Tamao, M. Kumada, *J. Organomet. Chem.* **1973**, *50*, C12–C14; b) M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 19505–19511; c) X.-W. Liu, J. Echavarren, C. Zarate, R. Martin, *J. Am. Chem. Soc.* **2015**,

137, 12470 – 12473; d) T. Niwa, H. Ochiai, Y. Watanabe, T. Hosoya, *J. Am. Chem. Soc.* **2015**, *137*, 14313 – 14318.
[27] A preliminary study showed that the catalysis is also valid for the intermolecular reactions: Unpublished results of Kayo Nakamura.
[28] A. E. Finholt, A. C. Bond, H. I. Schlesinger, *J. Am. Chem. Soc.* **1947**, *69*, 1199 – 1203.
[29] L. Crombie, G. W. Kilbee, G. Proudfoot, D. A. Whiting, *J. Chem. Soc. Perkin Trans. 1* **1991**, 3143 – 3148.
[30] Due to the enol ether substructure, the *exo* isomer was unstable to silica gel chromatography, thus leading to an impure material contaminated by some degradation products.
[31] a) G. M. Atkins, Jr., E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744 – 4745; b) E. M. Burgess, H. R. Penton, Jr., E. A. Taylor, *J. Org. Chem.* **1973**, *38*, 26 – 31.
[32] G. Blaskó, H.-L. Shieh, J. M. Pezzuto, G. A. Cordell, *J. Nat. Prod.* **1989**, *52*, 1363 – 1366.
[33] A sample of (−)-rotenone **1** was purchased from Sigma–Aldrich.

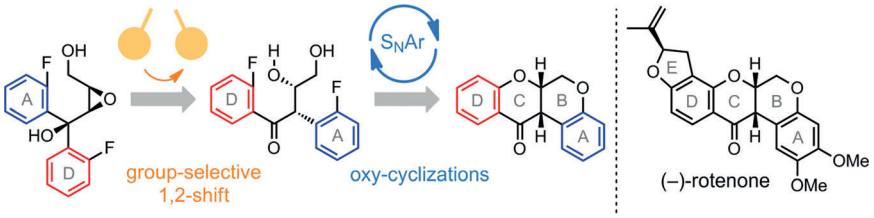
Manuscript received: September 21, 2016
Revised: November 1, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Natural Products

K. Nakamura, K. Ohmori,*
K. Suzuki* ——————— ■■■■–■■■■

Stereocontrolled Total Syntheses of (−)-Rotenone and (−)-Dalpanol by 1,2-Rearrangement and S_NAr Oxycyclizations



Shifty approach: An approach to the rotenoids is reported based on a stereospecific 1,2-shift of an epoxy alcohol followed by S_NAr oxycyclizations. The syntheses of the natural rotenoids, (−)-rotenone and (−)-dalpanol, have been achieved.