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Anion-Accelerated Aromatic Oxy-Cope Rearrangement in Geranylation/Nerylation of Xanthone: Stereochemical Insights and Synthesis of Fuscaxanthone F

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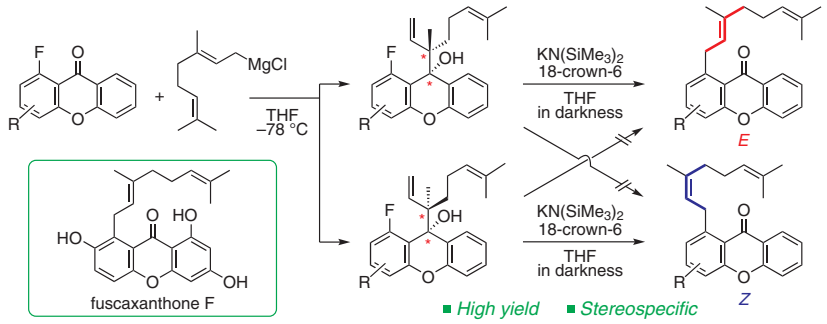

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Abstract An efficient installation of a 3,7-dimethylocta-2,6-dien-1-yl (geranyl or neryl) side chain at the C(1) position of a xanthone core by utilizing an anion-accelerated aromatic oxy-Cope rearrangement is described. Experiments revealed that this uncommon rearrangement takes place in a stereospecific manner through a chair-like transition-state structure. An application to the syntheses of the natural xanthone fuscaxanthone F, possessing a geranyl side chain, and its neryl analogue is also described.

Key words natural product synthesis, xanthones, oxy-Cope rearrangement, isoprenoids, geranylation, nerylation

Prenylated xanthones constitute the most abundant group of naturally occurring xanthones (Figure 1).[1–3] The pharmacological properties of these compounds vary markedly depending on the degrees and the patterns of prenyl substitution, as well as the length of each prenyl moiety.

During the course of our studies on the synthesis of biologically active xanthone derivatives,[4] we recently developed a novel two-step method for the installation of an isoprenyl (3-methylbut-2-en-1-yl) group at the C(1) [or C(8)] position of xanthones that utilizes an anion-accelerated aromatic oxy-Cope rearrangement (Scheme 1):[4b,c] Addition of an isoprenyl Grignard reagent to a 1-fluoroxanthone derivative **I** proceeds in a γ-selective manner. The resulting tertiary alcohol **II** undergoes anion-accelerated aromatic oxy-Cope rearrangement and subsequent elimination of fluoride ion under mild conditions to give the 1-isoprenylxanthone **III**. In addition to the broad substrate scope and high product yield of this method, the ready accessibility to a range of fluoroxanthone derivatives ensures its overall effectiveness.[5] Moreover, the unusual aromatic oxy-Cope rearrangement in which a π-bond of the aromatic ring participates as one of the ene partners in a 1,5-diene system pro-

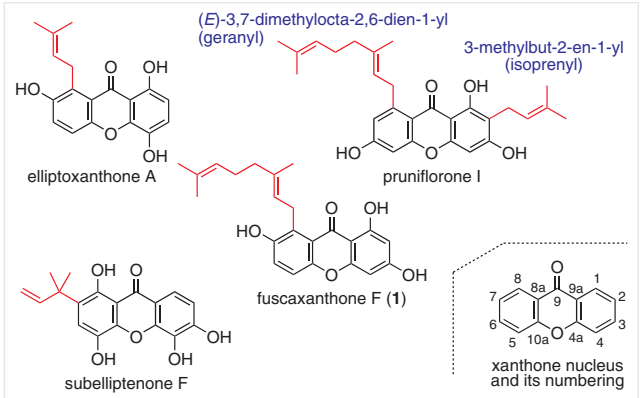
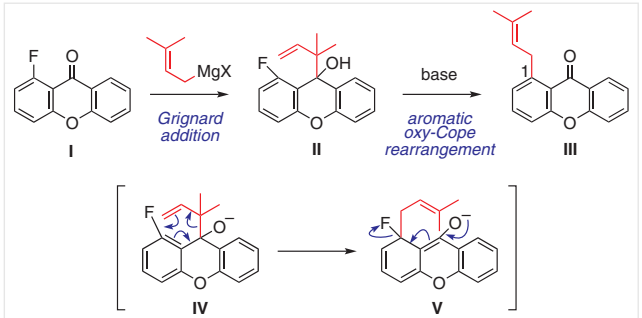


Figure 1 Examples of naturally occurring prenylxanthones



Scheme 1 Isoprenylation of the C(1) position of xanthone through the Grignard addition/anion-accelerated aromatic oxy-Cope rearrangement sequence starting from 1-fluoroxanthone derivative

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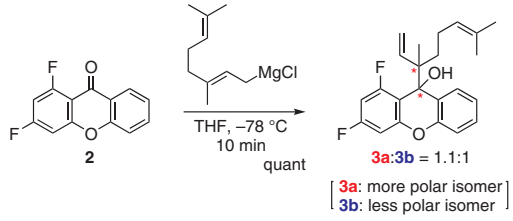
vides motivation for exploring further utilities of the reaction in synthesis and for gaining mechanistic insights.[6]

In this communication, we report the application of this method to the installation of geranyl [(*E*)-3,7-dimethylocta-2,6-dien-1-yl] or neryl [(*Z*)-3,7-dimethylocta-2,6-dien-1-yl] moieties. The experiments gave insights into the stereochemical course of the rearrangement; that is, the reaction proceeds in a stereospecific manner through a chair-like transition-state structure. Applications to the syntheses of fuscaxanthone F (**1**; Figure 1) and its *Z*-isomer are also described.

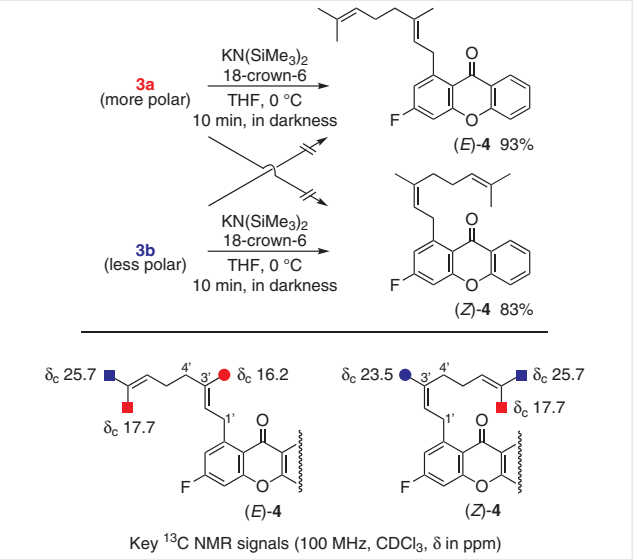
In an initial study, we employed 1,3-difluoroxanthone (**2**) as a model substrate, and we examined the addition of geranyl Grignard reagent (Scheme 2).[7] A solution of geranylmagnesium chloride in THF, prepared from geranyl chloride and magnesium turnings, was added to a THF solution of **2** at –78 °C. Xanthone **2** was consumed in 10 minutes at that temperature and gave a 1.1:1-mixture of diastereomers **3a** (more polar isomer) and **3b** (less polar isomer),[8] both arising from the expected γ-addition. These isomers were easily separable by silica-gel column chromatography, but we were unable to identify their stereostructures, largely because the two contiguous stereogenic carbons were both quaternary.



Scheme 2 Addition of geranyl Grignard reagent to 1,3-difluoroxanthone (**2**). See reference 8 for definitions of the terms 'more polar' and 'less polar'.

Next, the alcohols **3a** and **3b** were subjected to an oxy-Cope rearrangement under the conditions that we previously optimized for the installation of isoprenyl side chain [$KN(SiMe_3)_2$ (2.2 equiv), 18-crown-6 (3 equiv), THF, 0 °C, darkness] (Scheme 3).[4b,c,9] To our delight, each of the reactions completed quickly, giving high yields of the desired rearrangement products possessing a C_{10} side chain at the C(1) position. Furthermore, it turned out that the reactions were stereospecific; the isomeric alcohols **3a** and **3b** gave (*E*)-**4** and (*Z*)-**4**, respectively. No crossover [formation of (*E*)-**4** from **3b** or of (*Z*)-**4** from **3a**] was observed.

The configuration of the side chain (*E* or *Z*) was determined by extensive NMR study (see Supporting Information), and was corroborated by the well-proven rule for structural assignment of related systems based on the steric-compression effect.[10] The C(3)′-methyl carbon resonance of (*E*)-**4** (marked by a red solid circle; δ = 16.2 ppm)

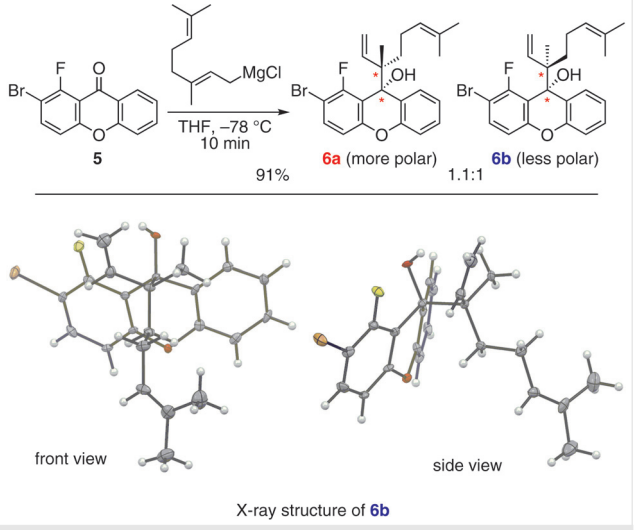


Scheme 3 Aromatic oxy-Cope rearrangements of isomeric alcohols **3a** and **3b**, and the key ^{13}C NMR signals for stereostructure assignment of the products on the basis of the steric-compression effect

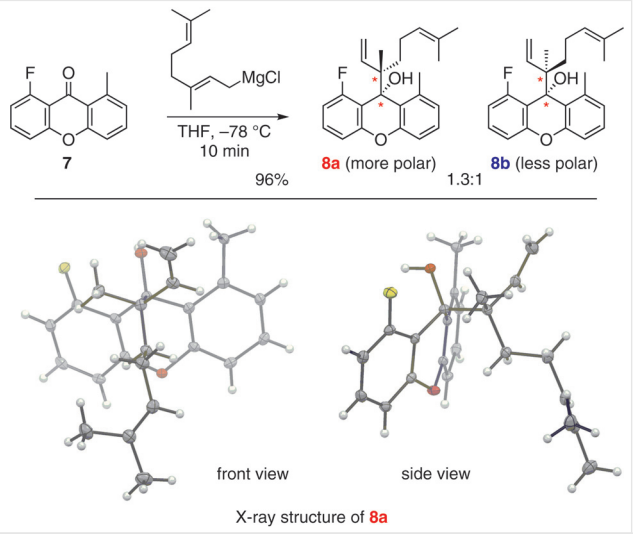
was significantly shifted upfield due to steric compression [cf. δ = 23.5 ppm for (*Z*)-**4** (marked by a blue solid circle)].

Further experiments were then carried out with some other 1-fluoroxanthone substrates to verify the stereospecific nature of the rearrangement and to determine its stereochemical course. This purpose was fulfilled by the use of 2-bromo-1-fluoroxanthone (**5**) and 1-fluoro-8-methylxanthone (**7**) as starting materials (Schemes 4 and 5, respectively).

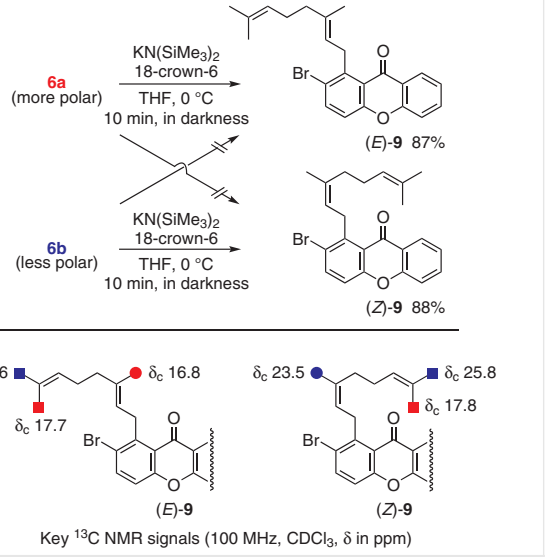
Reactions of **5** and **7** with geranyl Grignard reagent occurred in high yields, and the resulting isomeric alcohols



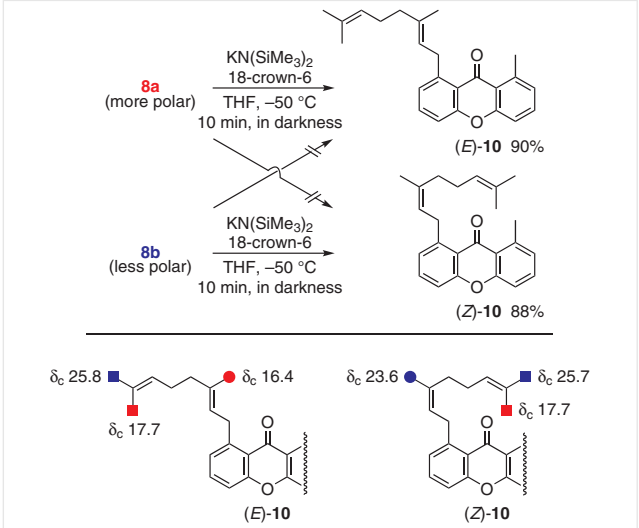
Scheme 4 Addition of geranyl Grignard reagent to 2-bromo-1-fluoroxanthone (**5**)



Scheme 5 Addition of geranyl Grignard reagent to 1-fluoro-8-methylxanthone (**7**)



Scheme 6 Aromatic oxy-Cope rearrangements of isomeric alcohols **6a** and **6b**



Scheme 7 Aromatic oxy-Cope rearrangements of isomeric alcohols **8a** and **8b**

were separable by silica-gel column chromatography in both cases. Furthermore, the less polar isomer **6b** arising from xanthone **5** and the more polar isomer **8a** arising from xanthone **7** were amenable to single-crystal X-ray diffraction analyses, leading to unambiguous determination of their stereostructures.[11] Consequently, the stereostructures of tertiary alcohols **6a** and **8b** were also specified definitely.

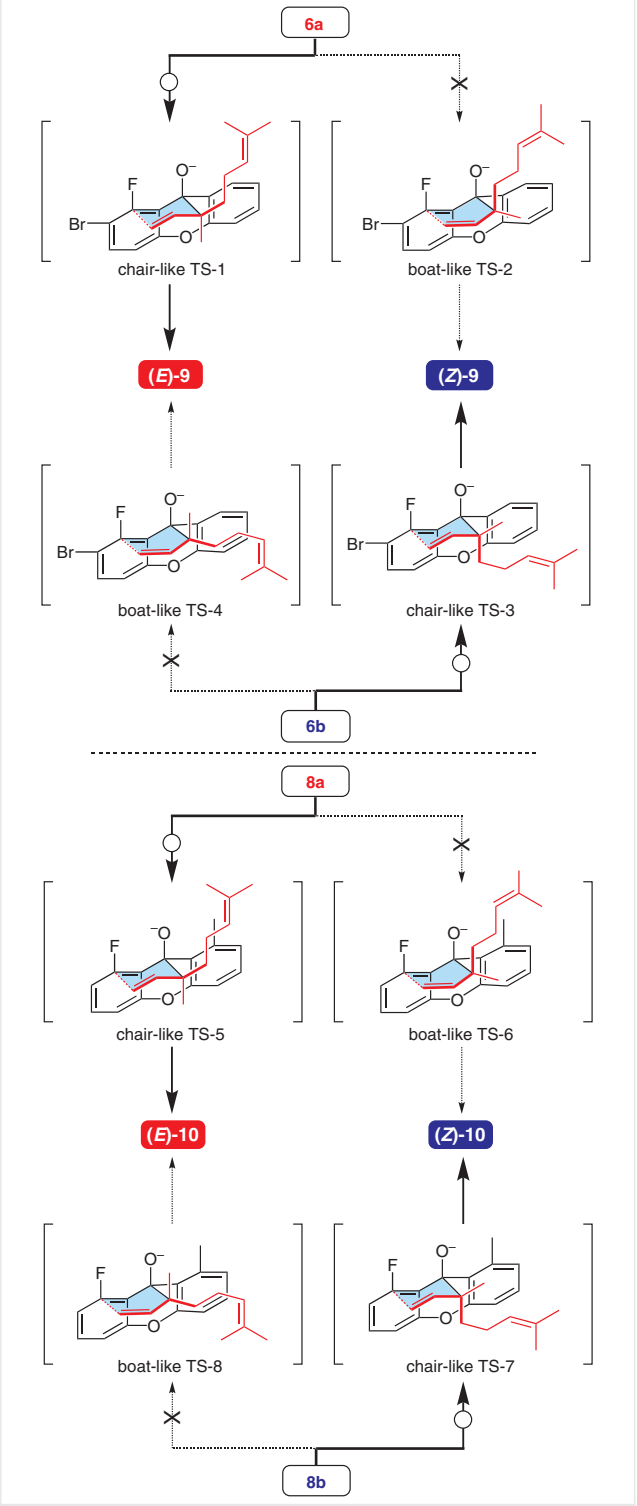
The tertiary alcohols, **6a**, **6b**, **8a**, and **8b** all underwent the oxy-Cope rearrangement rapidly and stereospecifically, as shown in Schemes 6 and 7.[12]

From these outcomes, it would be reasonable to assume a concerted character for the reaction and a chair-like transition-state structure thereof (Scheme 8).[13,14]

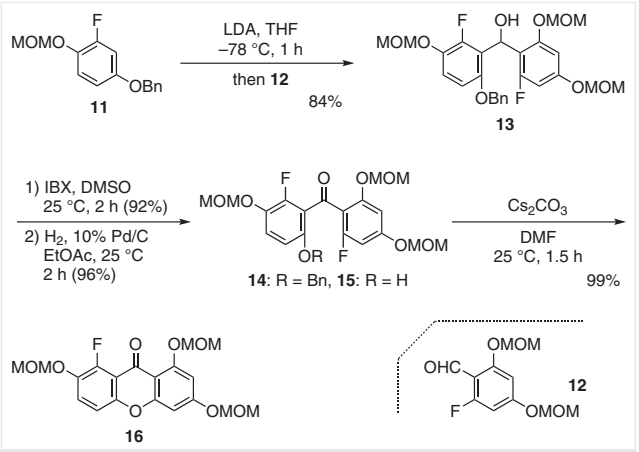
The application of the present method to the syntheses of fuscaxanthone F (**1**)[15] and its stereoisomer is described below. Fuscaxanthone F is a natural xanthone possessing a geranyl side chain at C(1), isolated by Ito and co-workers from *Garcinia fusca* Pierre, which is distributed in Asian countries and is known to be a rich source of biologically active prenylxanthones.[16]

The precursor for the installation of geranyl/neryl side chain, the fluoroxanthone **16**, was synthesized expeditiously from the readily accessible fluorobenzene derivatives **11**[4c] and **12**[17] (Scheme 9). *Ortho*-lithiation of **11** by LDA (–78 °C, 1 h) and subsequent addition of the resulting aryllithium to aldehyde **12** gave an 84% yield of alcohol **13**, which was then oxidized into the benzophenone **14** [2-iodoxybenzoic acid (IBX), DMSO, 25 °C, 2 h]. After removal of the benzyl group (H_2, 10% Pd/C, EtOAc, 25 °C, 2 h), cyclization of the resulting phenol **15** proceeded smoothly on treatment with Cs_2CO_3 in DMF at 25 °C to give the fluoroxanthone **16**.

Reaction of fluoroxanthone **16** with geranyl Grignard reagent went to completion quickly at –78 °C to give a mixture of diastereomers **17a** (more polar) and **17b** (less polar) in a ratio of 1.1:1 (Scheme 10). After separation (without determination of the stereostructures), each of the isomers was subjected to the oxy-Cope rearrangement with $KN(SiMe_3)_2$ and 18-crown-6 in THF at 0 °C. As expected, the reactions proceeded in high yields and in a stereospecific manner. Diastereomer **17a** exclusively gave xanthone (*E*)-**18** possessing a geranyl side chain, whereas **17b** exclusively gave (*Z*)-**18** possessing a neryl side chain. Finally, removal of

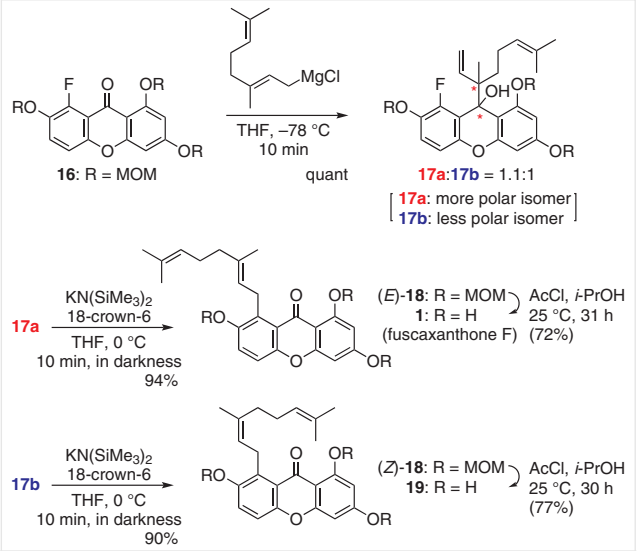


Scheme 8 Stereochemical course of the aromatic oxy-Cope rearrangement



Scheme 9 Synthesis of fluoroxanthone **16**

the MOM group from (*E*)-**18** by treatment with acetyl chloride in propan-2-ol at 25 °C for 31 h[4c,18] gave fuscaxanthone F (**1**) in 72% yield after purification by silica-gel chromatography. The reaction of (*Z*)-**18** under similar conditions (25 °C, 30 h) gave the *Z*-isomer **19** in 77% yield. Double-bond isomerization was not observed during the reactions. The spectral and physical properties of synthetic **1** (^{1}H and ^{13}C NMR, IR, and combustion analysis) were fully consistent with those of the natural product.



Scheme 10 Synthesis of fuscaxanthone F (**1**) and its *Z*-isomer (**19**)

In summary, an effective method for the installation of a 3,7-dimethylocta-2,6-dien-1-yl side chain at the C(1) position of a xanthone core was developed. Reactions of 1-fluoroxanthone derivatives with geranyl Grignard reagent took place in γ-selective manner to give approximately 1:1-mixtures of diastereomers that, in most cases, were isolable by silica-gel chromatography. Each of the isomers underwent

an oxy-Cope rearrangement cleanly under anion-accelerated conditions. Moreover, the rearrangement proved to be stereospecific. Each of the isomers allowed dependable formation of either of a geranyl or a neryl side chain. Precise stereochemical correlation between the rearrangement precursors and the products revealed a stereochemical course passing through a chair-like transition-state structure. The natural product fuscaxanthone F, possessing a geranyl side chain, and its neryl analogue were synthesized, demonstrating the utility of the method. As a result, both the geranylated and nerylated isomers of various xanthones are now accessible with stereochemical integrity. Needless to say, there are no known natural xanthones possessing a neryl side chain. This, in particular, is why the present method should provide a new opportunity for elucidating structure–activity relationships for prenylxanthone derivatives.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707117.

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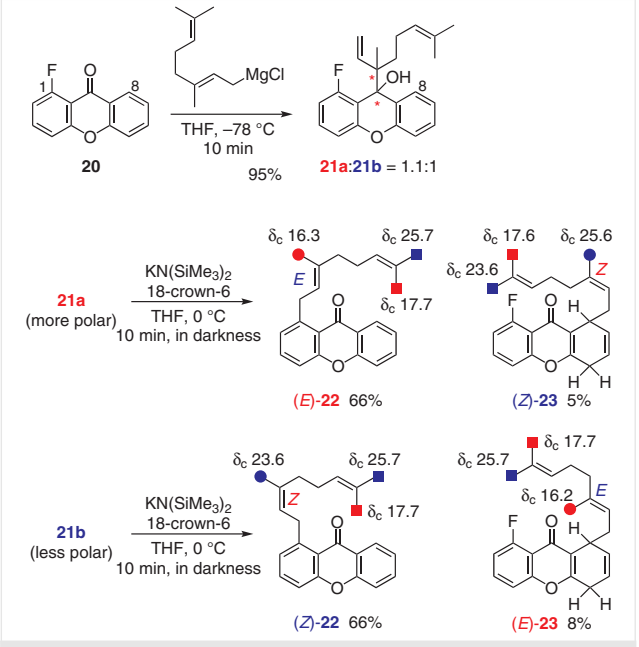
(7) To avoid confusing discussion, we opted not to record the results from the use of the parent compound 1-fluoroxanthone (**20**) as the starting material in the main text because of the formation of the byproducts (*Z*)- and (*E*)-**23** as a result of the migration of the C_{10} unit to the C(8) position (Scheme 11). Such migration to the undesired position did not occur when the starting xanthone was substituted by an inductively electron-withdrawing group at C(2) or C(3), as in **2** and **5**, or by an alkyl group at C(8), as in **7** (see ref. 4b). Nonetheless, it is worth



Scheme 11 The reaction of 1-fluoroxanthone (**20**)

noting that the reactions of alcohols **21a** and **21b** were both stereospecific: neither (*Z*)-**22** nor (*E*)-**23** was obtained from **21a** and, likewise, neither (*E*)-**22** nor (*Z*)-**23** was obtained from **21b**.

(8) Throughout this paper, 'more polar isomer' refers to the isomer of lower mobility on silica-gel TLC with hexane–EtOAc as eluent, and 'less polar isomer' refers to the isomer with a higher mobility.

(9) All the oxy-Cope rearrangements described in this paper were conducted in darkness in a brown-glass flask. Otherwise, many side reactions occurred, leading to irreproducible results. See ref. 4b.

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(11) CCDC 1989869 and 1989870 contain the supplementary crystallographic data for compounds **6b** and **8a**, respectively. The data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

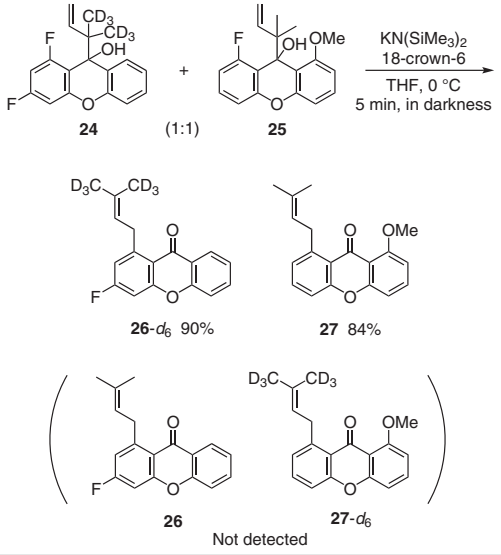
(12) **Grignard Addition/Aromatic Oxy-Cope Rearrangement Sequence: Synthesis of (*E*)-9; Typical Procedure**

A 1.0 M solution of geranyl Grignard reagent in THF (0.5 mL, 0.5 mmol) was added dropwise to a suspension of xanthone **5** (101 mg, 341 μmol) in THF (1.7 mL) at –78 °C, and the resulting mixture was stirred for 10 min at the same temperature. The reaction was then quenched with sat. aq NH_4Cl, and the 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 column chromatography [silica gel, hexane–EtOAc (7:1)] to give alcohol **6** as a mixture of diastereomers; yield: 134 mg (91%; **6a**/**6b** = 1.1:1). Further chromatographic separation [silica gel, hexane–EtOAc (40:1)] permitted the isolation of each of the isomers.

To a solution of **6a** (48.1 mg, 112 μmol) in THF (3.5 mL) in a two-necked brown-glass flask was added a 0.5 M solution of KHMDS in toluene (0.50 mL, 0.25 mmol), followed by a solution of 18-crown-6 (91.1 mg, 335 μmol) in THF (1.0 mL) at –78 °C. The reaction mixture was quickly warmed to 0 °C by replacing the dry ice–acetone bath with an ice-cold water bath, and stirring was continued for 10 min. The reaction was quenched with sat. aq NH_4Cl, and the 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 preparative TLC [silica gel, hexane–EtOAc (15:1)] to give xanthone (*E*)-**9** as a colorless oil; yield: 40.1 mg (87%).

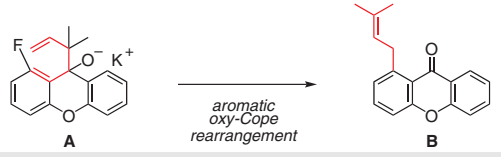
IR (neat): 2975, 2925, 2850, 1660, 1615, 1580, 1460, 1440 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 1.61 (d, *J* = 0.8 Hz, 3 H), 1.88 (d, *J* = 0.8 Hz, 3 H), 1.98–2.02 (m, 2 H), 2.04–2.10 (m, 2 H), 4.36 (d, *J* = 6.0 Hz, 2 H), 5.04–5.11 (m, 2 H), 7.24 (d, *J* = 8.8 Hz, 1 H), 7.34 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1 H), 7.41 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.68 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1 H), 7.84 (d, *J* = 8.8 Hz, 1 H), 8.28 (dd, *J* = 8.0, 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 17.7, 25.6, 26.7, 33.1, 39.8, 117.3, 117.9, 121.1 (2 C), 121.3, 122.6, 124.0, 124.4, 127.1, 131.1, 134.6, 136.3, 138.3, 143.9, 154.9, 156.9, 177.6. HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{23}BrNaO_2$: 433.0779; found: 433.0780.

(13) As additional information in this regard, a crossover experiment employing model compounds **24** and **25** demonstrated that the rearrangement occurred in an intramolecular manner, at least for the migration of C_5 (isoprenyl) moieties (Scheme 12).



Scheme 12 Crossover experiment

(14) Preliminary theoretical calculations for the migration of a C_5 unit as a model (Scheme 13) were carried out by density functional theory methods at the B3LYP/6–311+G(df,p)/THF(PCM) level of theory (*Gaussian 09* package). A very shallow bifurcation appeared on the potential-energy surface, suggesting that the rearrangement is not completely concerted. Accurate analysis indicated that bond dissociation precedes bond formation, and that a short-lived intermediate exists between them. See Supporting Information.



Scheme 13 Model reaction for theoretical calculations

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(16) For other examples of isolation of prenylxanthones from *G. fusca* Pierre, see: (a) Nontakham, J.; Charoenram, N.; Upamai, W.; Taweechotipatr, M.; Suksamrarn, S. *Arch. Pharmacal Res.* **2014**, *37*, 972. (b) Nguyen, N. K.; Truong, X. A.; Bui, T. Q.; Bui, D. N.; Nguyen, H. X.; Tran, P. T.; Nguyen, L.-H. D. *Chem. Biodivers.* **2017**, *14*, e1700232.

(17) See Supporting Information for the preparation of **12.**

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