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Synthesis of (−)-Flavoskyrins by Catalyst-Free Oxidation of (*R*)-Configured Dihydroanthracenones in Aqueous Media and Its (Bio)synthetic Implications

Amit Mondal, Arijit De, and Syed Masood Husain*

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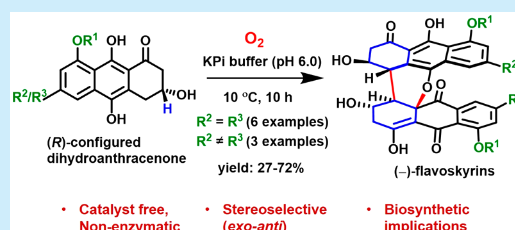
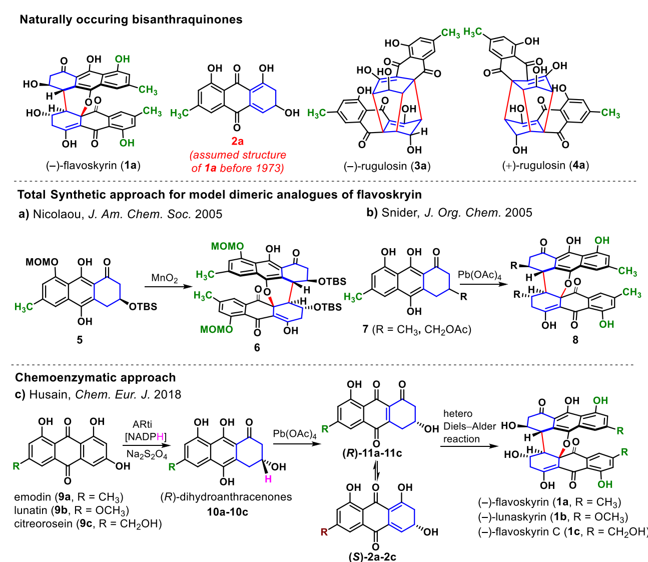
ABSTRACT: A catalyst-free method for the synthesis of dimeric (−)-flavoskyrins has been developed. It involves the autoxidation of chemoenzymatically synthesized (*R*)-configured dihydroanthracenones in the presence of molecular oxygen in buffer of pH 6.0 followed by spontaneous [4 + 2] cycloaddition in stereocontrolled *exo*-anti fashion to form (−)-flavoskyrins. The method is applied to obtain several homo- as well as heterodimerized flavoskyrins (nine examples) in 27−72% yield and implies the involvement of a similar pathway in the (bio)synthesis of modified bisanthraquinones and their analogues.



Nature produces a large number of dimeric natural products with novel structural features.[1,2] Among these, (−)-flavoskyrin (**1a**) possesses a unique molecular scaffold that has not yet been found in any other known natural products. Isolated first by Howard and Raistrick from *Penicillium islandicum* Sopp NRRL 1175 almost 70 years ago, it was thought to be a monomeric dihydroanthracendione **2a** (Scheme 1).[3−5] The structure was later revised by Shibata et al. to a dimeric compound represented by **1a**.[6] Interestingly, a biomimetic cascade conversion of (−)-flavoskyrin (**1a**) to a natural product, (−)-rugulosin (**3a**), in the presence of pyridine shown by Shibata further signifies its role as a biosynthetic intermediate (Scheme 1).[6] Therefore, a flavoskyrin-type compound has also been proposed to be involved in the biosynthesis of (+)-rugulosin (**4a**), which has been isolated from several fungi.[7] This inspired Nicolaou and coworkers to synthesize (+)-rugulosin (**4a**) using a protected flavoskyrin-type compound **6**, which was synthesized by the oxidation of dihydroanthracenone **5** using MnO_2.[8] A similar strategy was used by Snider and coworkers to obtain dimeric flavoskyrin **8** through the oxidation of dihydroanthracenone **7** by $Pb(OAc)_4$ (Scheme 1).[9] However, (−)-flavoskyrin (**1a**) could not be synthesized using the above methods due to the presence of a chemically sensitive *β*-hydroxy ketone group in both of the monomeric tricyclic units, which easily undergoes water elimination.[10] To overcome these difficulties, we developed a chemoenzymatic method that successfully led us to synthesize (−)-flavoskyrin (**1a**). It required the oxidation of (*R*)-3,8,9,10-tetrahydroxy-6-methyl-3,4-dihydroanthracen-1(2*H*)-one (**10a**, R = CH_3), which was obtained by the chemoenzymatic reduction of emodin (**9a**) catalyzed by the 17*β*-hydroxysteroid dehydrogenase of *Cochliobolus lunatus* (17*β*-HSDcl) using NADPH in the presence of $Na_2S_2O_4$ (Scheme 1).[11]

The detailed investigation shows that (*R*)-**10a** on oxidation with $Pb(OAc)_4$ in AcOH forms a mixture of (*R*)-3,4-dihydroemodin (**11a**, R = CH_3) and its dienol tautomer (*S*)-

Scheme 1. Monomeric and Dimeric Anthraquinones and Their Synthesis



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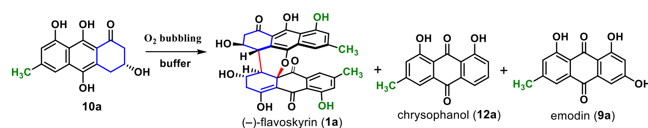
2a (R = CH_3) that acts as a monomeric precursor for dimerization to (−)-flavoskyrin. Hence the spontaneous dimerization between two monomeric **2a** in a stereocontrolled *exo*-anti fashion following a [4 + 2] hetero-Diels−Alder reaction forms (−)-flavoskyrin (**1a**).[11] This simple chemoenzymatic approach not only gave access to the putative biosynthetic intermediates (*S*)-**2a** and (*R*)-**11a** for the first time but also implicated the role of (*R*)-**10a** as an intermediate in the (bio)synthesis of (−)-flavoskyrin (**1a**) and (−)-rugulosin (**3a**) (Scheme 1).[11] Likewise, lunatin (**9b**, R = OCH_3) and citreorosein (**9c**, R = CH_2OH) were used to obtain (−)-lunaskyrin (**1b**)[11] and (−)-flavoskyrin C (**1c**),[12] respectively (Scheme 1c). The spontaneous nature of stereocontrolled dimerization in the above process motivated us to investigate the catalyst-free oxidation of (*R*)-**10a** for the synthesis of (−)-flavoskyrin (**1a**) under aqueous ambient conditions. This might provide vital clues on how (−)-flavoskyrin (**1a**) is biosynthesized and why no flavoskyrin-type molecule other than **1a** has been isolated from natural sources.

Considering the involvement of the oxidation of hydroanthraquinone (*R*)-**10a** to an anthraquinone (*R*)-**11a**, we asked if this could be achieved through the process of autoxidation. The autoxidation of hydroquinone to quinone plays a significant role in biological systems during redox cycling[13] as well as in biosynthesis.[14] For example, during melanin biosynthesis, the key metabolites such as flaviolin and 2-hydroxyjuglone have been proposed as being formed through the oxidation of their precursors, 1,3,6,8-tetrahydroxynaphthalene and 1,6,8-trihydroxynaphthalene, respectively, without the involvement of an enzyme.[14] In another example, the process of the autoxidation of 2-alkyl-9,10-anthrahydroquinone to its anthraquinone in the presence of molecular oxygen is used during the industrial production of hydrogen peroxide.[15] Likewise, we propose that similar autoxidation might convert the hydroanthraquinone (*R*)-**10a** to the anthraquinone (*R*)-**11a** using molecular oxygen, which on tautomerization to (*S*)-**2a** under appropriate conditions will spontaneously dimerize to form (−)-flavoskyrin (**1a**).

To prove our hypothesis, we used (*R*)-**10a** as a model substrate, which was synthesized through the chemoenzymatic reduction of emodin (**9a**) using an anthrol reductase from *Talaromyces islandicus* (ARti) and NADPH in the presence of $Na_2S_2O_4$.[16] At first, (*R*)-**10a** dissolved in acetonitrile (30% v/v) was incubated in potassium phosphate buffer (50 mM KPi, pH 7.0) under an oxygen atmosphere for 2 h. The reaction mixture was analyzed using reverse-phase HPLC, which revealed the formation of the expected deoxyanthraquinone, chrysophanol (**12a**) and the oxidized product, emodin (**9a**), in a 53:47 ratio with 77% conversion (Table 1, entry 1). However, no (−)-flavoskyrin (**1a**) was formed, which could be due to the nonmixing of molecular oxygen. Therefore, we performed the above reaction by bubbling molecular oxygen into the reaction system. This resulted in the formation of (−)-flavoskyrin (**1a**) along with **12a** and **9a** in a 13:43:44 ratio with 70% conversion (Table 1, entry 2). Also, considering the role of the pH in tautomerism, which could affect the dimerization to (−)-flavoskyrin (**1a**), we incubated (*R*)-**10a** in buffer of pH 5.0, 5.5, 6.0, 6.5, and 8.0 (Table 1, entries 3−7) and bubbled molecular oxygen into the reaction mixture for 2 h. We observed 45% conversion of (*R*)-**10a** to products at pH 5.0 (Table 1, entry 3). However, the reactions performed at pH 5.5, 6.0, and 6.5 gave nearly 98% conversion with (−)-flavoskyrin (**1a**) as a major product (Table 1, entries 4−6). However, the further increase in pH to 8.0 did not yield (−)-flavoskyrin (**1a**) in the reaction (Table 1, entry 7). This indicates that an acidic pH facilitates the formation of tautomer (*S*)-**2a** of (*R*)-3,4-dihydroemodin (**11a**) that is formed by the oxidation of (*R*)-**10a** in the presence of molecular oxygen. This is followed by the spontaneous cycloaddition between the two monomeric (*S*)-**2a** to form dimeric (−)-flavoskyrin (**1a**). Under a basic pH, (*R*)-3,4-dihydroemodin (**11a**) mainly dehydrates to form chrysophanol (**12a**). We also used Tris-HCl buffer (50 mM, pH 6.0) instead of KPi buffer, but it resulted in a reduced conversion to products (Table 1, entry 8). In addition, we tested 2-propanol, 1,4-dioxane, acetone, and DMSO as cosolvents in buffer (50 mM KPi, pH 6.0). The results show reduced conversion to **1a** in the case of 2-propanol and 1,4-dioxane, whereas the use of acetone and DMSO gave comparable conversion to that of acetonitrile (see the Supporting Information (SI), Table S1, entries 1−5). Next, we look at the effect of concentration on the formation of **1a**. The reactions with concentration of 0.5 and 2 mg/mL of (*R*)-**10a** gave 68 and 72% of **1a**, respectively (overall conversion 97%) (Table 1, entries 9 and 10). However, the concentration of 4 mg/mL gave 69% of **1a** but reduced the overall conversion to 78%, which could be due to the low solubility of (*R*)-**10a** (Table 1, entry 11).

Table 1. Optimization of (−)-Flavoskyrin (1a) Synthesis through Autoxidation of (*R*)-10a[a]



entry	pH	conc.(mg/mL)	time (h)	conv. (%)	ratio (1a/12a/9a)
1[b]	7	1	2	77	−:53:47
2	7	1	2	70	13:43:44
3	5	1	2	45	49:30:21
4	5.5	1	2	97	70:18:12
5	6	1	2	98	71:20:9
6	6.5	1	2	98	70:20:10
7	8	1	2	71	−:47:53
8[c]	6	1	2	72	62:24:14
9	6	0.5	2	97	68:25:7
10	6	2	2	97	72:17:11
11	6	4	2	78	69:14:17
12[d]	6	2	4	99	79:14:7
13[d,e]	6	2	10	99	79:12:9

[a]All conversions and ratios are based on reverse-phase HPLC using questin as an internal standard. [b]Under an oxygen atmosphere. [c]tris-HCl buffer (50 mM, pH 6). [d]At 10 °C. [e]1 mmol scale reaction.

To further reduce the formation of side products, we incubated (*R*)-**10a** under the same conditions as entry 10 (Table 1) but at a lower temperature (10 °C). This resulted in the formation of (−)-flavoskyrin (**1a**), chrysophanol (**12a**), and emodin (**9a**) in a 79:14:7 ratio with 99% overall conversion (Table 1, entry 12). However, further lowering of temperature reduces the overall conversion (see Table S1, entry 6). Finally, a large-scale reaction was performed; taking 1 mmol of (*R*)-**10a** under the same conditions yielded **1a**, **12a**, and **9a** in a 79:12:9 ratio with 99% conversion after 10 h (Table 1, entry 13). The purification using oxalic-acid-impregnated silica gel resulted in the isolation of (−)-flavoskyrin (**1a**), chrysophanol (**12a**), and emodin (**9a**) in 72, 10, and 6% yield, respectively. This is similar to the previously

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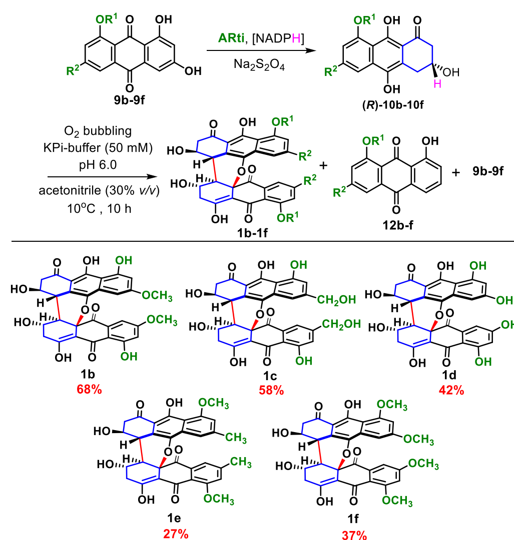
Org. Lett. XXXX, XXX, XXX−XXX

reported yield obtained by the oxidation of (R)-**10a** using $Pb(OAc)_4$.[11]

In most of the cases above, the monomeric intermediates (S)-**2a**/(R)-**11a** were observed only in HRMS and not in ^{1}H NMR spectra. This could be due to the spontaneous cycloaddition of dienol tautomer (S)-**2a** of 3,4-dihydroemodin (R)-**11a**, formed by the oxidation of (R)-**10a**. This is in contrast with the use of $Pb(OAc)_4$ as an oxidizing agent (Scheme 1c), where (R)-**10a** completely oxidizes to (R)-**11a.**[11] Accordingly, we propose that the biosynthesis of (−)-flavoskyrin (**1a**) would involve the reduction of emodin (**9a**) to (R)-**10a** by the enzymes using NADPH in the first step. This is followed by the non-enzymatic autoxidation of (R)-**10a** to dihydroemodin (R)-**11a**, which, on tautomerism, will form dienol tautomer (S)-**2a** and will spontaneously dimerize following a [4 + 2] hetero-Diels−Alder reaction to form (−)-flavoskyrin (**1a**).

To further expand the scope of the current method and get clues about the stability and the ease of formation of other flavoskyrin-type compounds, we aimed to prepare various homo- as well as heterodimeric analogues of (−)-flavoskyrin (**1a**). For this purpose, we synthesized lunatin (**9b**, R^1 = H, R^2 = OCH_3), citreorosein (**9c**, R^1 = H, R^2 = CH_2OH), 1,3,6,8-tetrahydroxyanthraquinone (**9d**, R^1 = H, R^2 = OH), and 1-methyl emodin (**9e**, R^1 = CH_3, R^2 = CH_3) using a previously reported procedure.[16] In addition, we also synthesized 1-methyllunatin (**9f**, R^1 = CH_3, R^2 = OCH_3) to be tested as a substrate with the enzyme (Scheme 2) (see the SI).

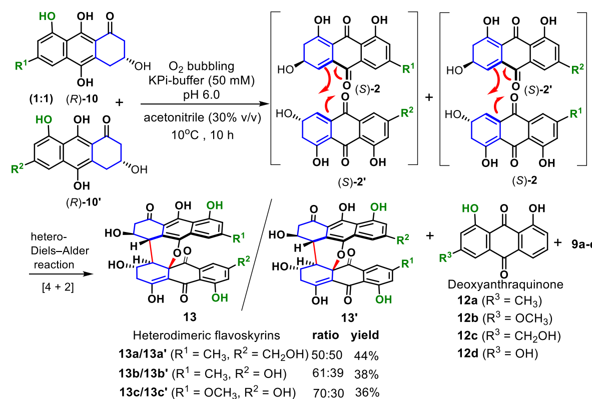
Scheme 2. Synthesis of Homodimerized Flavoskyrin Analogues and Deoxyanthraquinones



The anthraquinones **9b−f** were then chemoenzymatically reduced using ARti in the presence of $Na_2S_2O_4$ to obtain (R)-configured dihydroanthracenones **10b−f** (Scheme 2). When **10b** (R_1 = H, R_2 = OCH_3) was incubated in KPi buffer (50 mM, pH 6.0) for 10 h at 10 °C under oxygen bubbling conditions, the expected products, (−)-lunaskyrin (**1b**), 3-methoxychrysazine (**12b**, R^1 = H, R^2 = OCH_3), and lunatin (**9b**), were obtained after purification using oxalic-acid-impregnated silica gel in 68, 12, and 8% yield, respectively. Likewise, (−)-flavoskyrin C (**1c**) was obtained in 58% yield by the homodimerization of **10c** (R^1 = H, R^2 = CH_2OH) along with aloe-emodin (**12c**, R^1 = H, R^2 = CH_2OH) in 18% yield and a small amount of citreorosein (**9c**) (Scheme 2). For other flavoskyrin analogues, we incubated (R)-**10d** (R^1 = H, R^2 = OH) under optimized conditions. The expected flavoskyrin-type compound **1d** was isolated in 42% yield along with deoxyanthraquinone **12d** (R^1 = H, R^2 = OH) in 20% yield and a small amount of **9d** (Scheme 2). The lower yields could be due to the low solubility of (R)-**10d** in acetonitrile pertaining to the presence of many hydroxyl groups. Furthermore, dihydroanthracenones (R)-**10e** (R^1 = CH_3, R^2 = CH_3) and (R)-**10f** (R^1 = CH_3, R^2 = OCH_3) were used to synthesize flavoskyrin-type compounds **1e** and **1f** in 27 and 37% yield, respectively (Scheme 2). The reaction also resulted in the isolation of deoxyanthraquinone **12e** (R^1 = CH_3, R^2 = CH_3) and **12f** (R^1 = CH_3, R^2 = OCH_3) in 14 and 12% yield, respectively, along with a small amount of the respective anthraquinones (Scheme 2). Lower yields might be due to a less efficient cycloaddition reaction caused by the steric hindrance owing to the presence of methoxy groups in (R)-**10e** and (R)-**10f**.

Next, we focused on synthesizing heterodimeric flavoskyrins. For this purpose, a mixture of (R)-**10a** (R^1 = CH_3) and (R)-**10c** (R^2 = CH_2OH) taken in the ratio of 1:1, was dissolved in acetonitrile (30% v/v) and incubated under the optimized conditions for 10 h (Scheme 3). This resulted in the isolation

Scheme 3. Synthesis of Heterodimerized Flavoskyrin Analogues



of an inseparable mixture of the heterodimerized (−)-flavoskyrins B (**13a**) and B′ (**13a′**) in a 50:50 ratio in 44% isolated yield after purification with oxalic-acid-impregnated silica gel (Scheme 3). The two diastereomeric flavoskyrins, **13a** and **13a′**, were formed by the hetero-Diels−Alder reaction between two different dienol tautomers acting as both a dienophile as well as a diene (see the SI). In addition, we also obtained homodimerized (−)-flavoskyrin (**1a,** R^1 = R^2 = CH_3) and (−)-flavoskyrin C (**1c**, R^1 = R^2 = CH_2OH), deoxyanthraquinones **12a** (R^3 = CH_3) and **12c** (R^3 = CH_2OH), and respective anthraquinones in minor amounts (Scheme 3) (see Figure S4).

Likewise, a mixture of (R)-**10a** (R^1 = CH_3) and (R)-**10d** (R^2 = OH) taken in 1:1 ratio was prepared in acetonitrile (30% v/v), and a few drops of DMSO were added to dissolve it completely (Scheme 3). After incubation under the optimized conditions for 10 h, we could isolate a mixture of the heterodimerized flavoskyrins **13b**/**13b′** (61:39) in 38% yield along with a small amount of the expected homodimerized flavoskyrins **1a** and **1d** (R^1 = R^2 = OH), deoxyanthraquinones **12a** and **12d**, and respective anthraquinones (Scheme 3).

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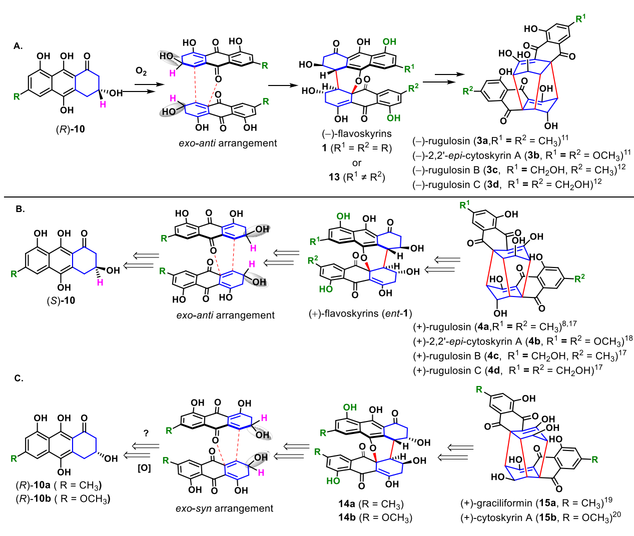
Org. Lett. XXXX, XXX, XXX−XXX

Similarly, (*R*)-**10b** (R^1 = OCH_3) and (*R*)-**10d** (R^2 = OH) taken in 1:1 ratio were oxidized to obtain a mixture of flavoskyrins **13c**/**13c′** (70:30) in 36% yield, along with flavoskyrins **1b** (R^1 = R^2 = OCH_3) and **1d**, deoxyanthraquinones **12b** and **12d**, and the respective anthraquinones, as expected (Scheme 3). Our attempts to obtain other heterodimerized flavoskyrins resulted in an inseparable mixture of homo- as well as heterodimerized flavoskyrins and hence were not purified.

The above examples demonstrate that (−)-flavoskyrins like **1** or **13** can be obtained successfully by the autoxidation of (*R*)-configured dihydroanthracenones followed by spontaneous cycloaddition in an *exo*-anti fashion under mild aqueous conditions and hence might take place non-enzymatically during biosynthesis (Scheme 4A). Because our study supports the presence of other flavoskyrin-type molecules in nature, we believe that the reason not many of them have been isolated yet is due to the presence of the chemically sensitive β-hydroxy ketone group. Nevertheless, the flavoskyrins such as **1b**, **1c**, and **13a**/**13a′** can be utilized toward the (bio)synthesis of bisanthraquinones such as (−)-2,2′-*epi*-cytoskyrin (**3b**),[11] (−)-rugulosin C (**3c**),[12] and (−)-rugulosin B (**3d**),[12] which are yet to be isolated from natural sources (Scheme 4A).

Scheme 4. Proposed Synthesis of Plausible Stereoisomers of (−)-Flavoskyrins and their (Bio)synthetic Implications for Modified Bisanthraquinones



Furthermore, considering the stereochemistry of the known bisanthraquinones, we propose the existence of two other types of flavoskyrins in nature. One is (+)-flavoskyrins like *ent*-**1**, which may act as intermediates in the (bio)synthesis of naturally occurring (+)-rugulosin (**4a**),[6,17] (+)-2,2′-*epi*-cytoskyrin (**4b**),[18] (+)-rugulosin B (**4c**),[17] and (+)-rugulosin C (**4d**) (Scheme 4B).[15] Here *ent*-**1** can be formed by the oxidation of (*S*)-configured dihydroanthracenones (*S*)-**10** followed by stereocontrolled cycloaddition in an *exo*-anti fashion (Scheme 4B). However, the enzyme(s) that can catalyze the chemoenzymatic reduction of anthraquinones to (*S*)-configured dihydroanthracenones are yet to be identified.

The second type of flavoskyrins is represented by structure **14a,b** and might be involved in the (bio)synthesis of (+)-graciliformin (**15a**)[19] and (+)-cytoskyrin A (**15b**) (Scheme 4C).[20] However, this would require the oxidation of (R)-configured dihydroanthracenones, followed by the cycloaddition in an *exo*-syn fashion. This may give bisanthraquinones in which the two hydroxyl groups are present on the same side in a more crowded arrangement (Scheme 4C). Because the non-enzymatic oxidation of (*R*)-**10** followed by spontaneous dimerization exclusively gave (−)-flavoskyrins we believe that the dimerization with *exo*-syn cycloaddition might be enzymatic.

In conclusion, a greener, biomimetic method for the synthesis of dimeric, homo- as well as heterodimerized (−)-flavoskyrins has been developed. It relies on the autoxidation of (*R*)-configured dihydroanthracenones and supports the role of non-enzymatic oxidation during flavoskyrin biosynthesis, as postulated for several natural products by Gravel and Poupon.[21] The work also proposed the existence of diastereomeric flavoskyrins such as *ent*-**1** and **14a,b** as biosynthetic intermediates that may be isolated in future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03121.

Procedures and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Syed Masood Husain − *Molecular Synthesis and Drug Discovery Unit, Centre of Biomedical Research, Lucknow 226014, India*; orcid.org/0000-0002-4698-475X; Email: smhusain@cbmr.res.in, smhusain.cbmr@gmail.com

Authors

Amit Mondal − *Molecular Synthesis and Drug Discovery Unit, Centre of Biomedical Research, Lucknow 226014, India*

Arijit De − *Molecular Synthesis and Drug Discovery Unit, Centre of Biomedical Research, Lucknow 226014, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03121

Notes

The authors declare no competing financial interest.

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