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Studies Directed towards the Synthesis of the Acridone Family of Natural Products: Total Synthesis of Acronycines and Atalaphyllidines

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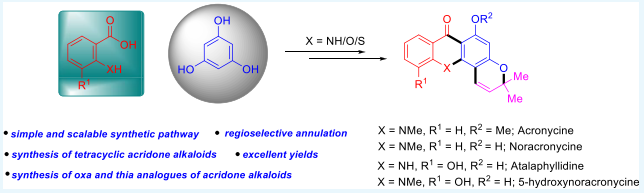
ABSTRACT: A modular and flexible three-step synthetic strategy has been developed for the synthesis of acridone natural products of biological significance. The tetracyclic core of acridone derivatives has been achieved efficiently in high yield from commercially available anthranilic acid and phenol derivatives via condensation reaction, followed by regioselective annulation. Acridone alkaloids acronycine and noracronycine are synthesized in improved overall yields in fewer steps than the previously reported approaches. The method has further been used for the synthesis of atalaphyllidine and 5-hydroxynoracronycine in excellent yields for the first time. Moreover, the synthetic utility of the present strategy has been showcased by the synthesis of oxa and thia analogues of acronycine alkaloid.



INTRODUCTION

Acridone alkaloids represent a large panel of biologically active compounds[1] and exhibit a wide spectrum of biological activities ranging from antitumor, anticancer[2] to antiviral[3] and antimalarial properties.[4] Among these alkaloids, acronycine, a pyranoacridone alkaloid (Figure 1) isolated from the Australian scrub ash *Baurella simplicifolia* (Endl.) Hartley (Rutaceae),[5] exhibits the broadest spectrum of in vivo antineoplastic activity.[1c,6] Noracronycine was isolated from *Medicosma subsessilis* (Figure 1).[7] Recently, two new polycyclic acridone alkaloids, chlorospermine A and B, along with atalaphyllidine and acrifoline have been isolated from the stem bark of *Glycosmis Chlorosperma* (Figure 1).[8] Among them, chlorospermine B possesses significant inhibitory property against dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A).[8] Although several approaches have been developed over the years for the synthesis of various acridone alkaloids and their analogues;[9−12] implementation of an efficient and modular synthetic route to acridone derivatives holds a high significance. Especially, the reported approaches do not provide the central core with a fully functionalized **A** ring, and a structure−activity study using various functional groups to access ring **A** is still missing.

The reported synthesis of various acridone derivatives is mainly based on Friedel−Crafts reactions of electron-rich arenes under strongly acidic conditions.[9,10] The Claisen rearrangement-based approach has been reported using 3-chloro-3-methylbut-1-yne to synthesize tetracyclic acridone derivatives from tricyclic dihydroxy acridones.[11] In a different method developed by Kolokythas and co-workers, the reaction of methyl 3,5-dihydroxybenzoate with 3-chloro-3-methyl-1-butyne provided the corresponding chromene derivative, which on treatment with 2-chloronicotinic acid followed by cyclization furnished the desired acridone derivative.[12a] Recently, Maji and co-workes developed a cobalt-catalyzed amidation protocol that gives access to acridone-based natural products efficiently.[12b] Zheng et al. developed a one-pot synthesis of 1-hydroxyacridones via the DBU-mediated reaction of quinols and ortho-methoxycarbonylaryl isocyanates following a sequence of intramolecular condensation, tautomerization, and decarboxylation.[12c] Zyryanov and co-workers developed a new method for the synthesis of cytotoxic tetracyclic acridone derivatives and further evaluated their bioactivity and protein-binding properties by biological and biophysical studies.[12d]

RESULTS AND DISCUSSION

We envisioned developing a linear yet efficient synthetic route for the preparation of tetracyclic acridone alkaloids. We hypothesized that tetracyclic acridone alkaloids **1** can be synthesized by selective protection and deprotection of the cyclic precursor **2**. The **D** ring could be installed via titanium isopropoxide-mediated regioselective annulation of 1,3-dihydroxyacridone derivative **4** with prenal **3**.[13] The dihydroxy

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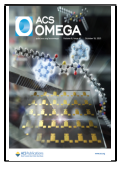


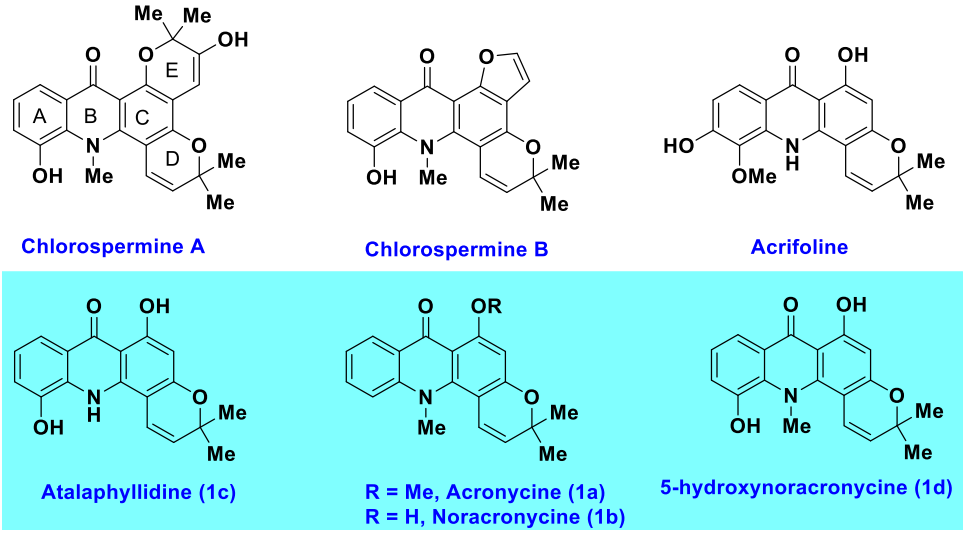
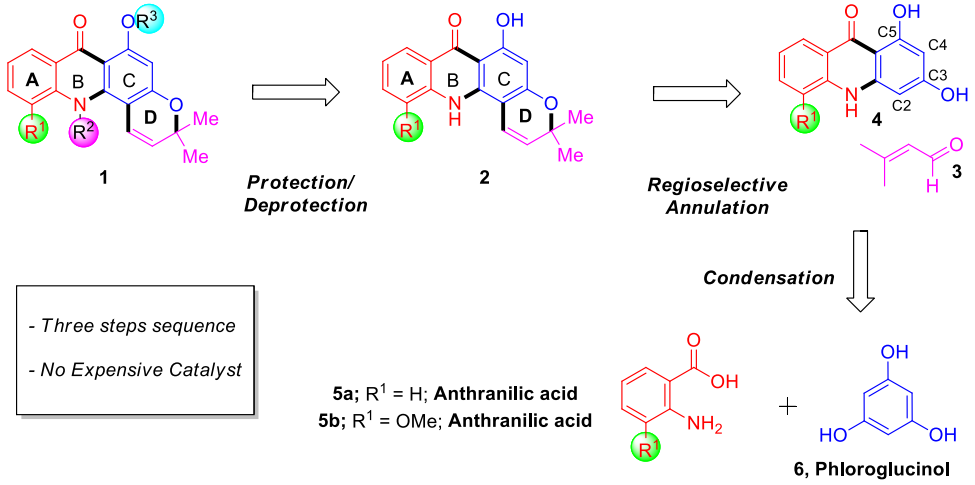


Figure 1. Some representative acridone alkaloids.

Scheme 1. Our Retrosynthetic Analysis



intermediate **4** could be easily accessed by condensation of **5** and **6** (Scheme 1).[14]

We have first set our goal towards the synthesis of acronycine **1a** and noracronycine **1b** (Scheme 2). The condensation of anthranilic acid **5a** and phloroglucinol **6** in the presence of the catalytic amount of TsOH in *n*-hexanol provided the 1,3-dihydroxyacridone derivative **4a** in excellent yield.[14] The product was obtained in pure form by filtration without chromatographic purification. As per our plan, the $Ti(OiPr)_4$-mediated regioselective annulation of **4a** with prenal **3** was next carried out to obtain the desired tetracyclic compound **2a** in excellent yield (Scheme 2).[13]

The regioselective cyclization involves the sole participation of the C3-OH group of **4a**, which may be attributed to the strong intramolecular H-bonding between the carbonyl group and the C5-OH group (Figure 2). The treatment of **2a** with excess of methyl iodide provided acronycine **1a** in almost quantitative yield. A subsequent BBr_3-mediated demethylation resulted in noracronycine **1b** in excellent overall yield (Scheme 2).

The synthesis of acronycine and noracronycine was first reported by Beck and co-workers via the formation of dihydronoracronycine, which upon oxidation followed by methylation provided noracronycine and acronycine, respectively.[15] Reisch et al. synthesized noracronycine analogues by the reaction of the *N*-methyl-1,3-dihydroxyacridone derivative with propinols under Mitsunobu condition.[16] Recently, Lee and co-workers reported the synthesis of acronycine and noracronycine via ethylenediamine diacetate-mediated cyclization of the dihydroxyacridone derivative followed by selective methylation.[17] In our approach, we have successfully accomplished the synthesis of acronycine and noracronycine in a comparatively lesser number of steps with an improvement in overall yields.

With the success of our designed protocol, our goal was to validate our strategy for a concise total synthesis of atalaphyllidine **1c** and 5-hydroxynoracronycine **1d**. To date, no synthetic routes have been reported for the synthesis of these two acridone alkaloids. In order to obtain these acridone derivatives, we started our synthetic journey with 2-amino-3-methoxybenzoic acid **5b** instead of anthranillic acid **5a** as used previously. The reaction of **5b** with **6**, under refluxing conditions, provided the desired dihydroxyacridone derivative **4b** in high yield (Scheme 3). The regioselective annulation of **4b** using titanium isopropoxide and prenal **3** gave rise to the requisite tetracyclic acridone derivative **2b**, a suitable precursor for the synthesis of atalaphyllidine **1c** and 5-hydroxynoracro-

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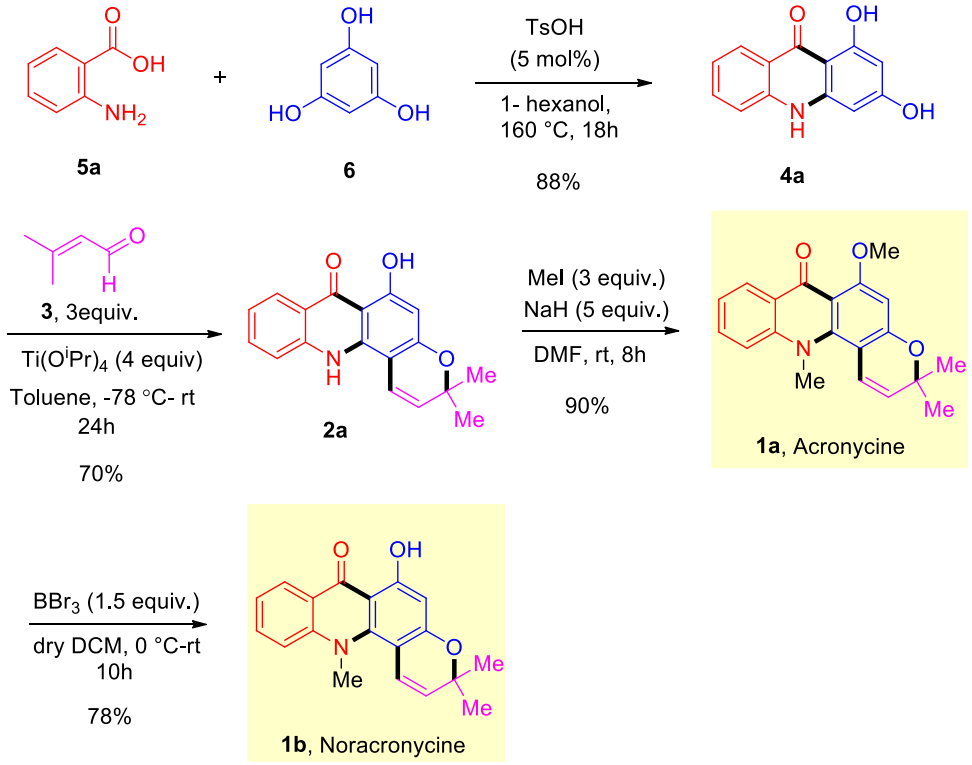
Scheme 2. Synthesis of Acronycine and Noracronycine



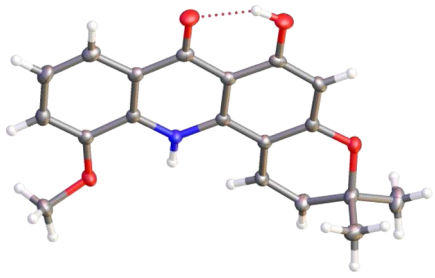


Figure 2. X-ray crystal structure of compound 2b.

nycine **1d** (Scheme 3). The treatment of **2b** with BBr_3 in dichloromethane successfully afforded atalaphyllidine **1c** in excellent yield. Compound **2b** could also be converted to 5-hydroxynoracronycine **1d** via a two-step process as shown in Scheme 3. The reaction of **2b** with excess methyl iodide provided the *N*- and *O*-methyl protected acridone intermediate, which was directly treated with BBr_3 to obtain the desired product **1d** in good isolated yield (Scheme 3). The ^1H and ^{13}C NMR spectra of **1c** and **1d** match with the reported spectra.[18,19]

It is intriguing to mention here that the intramolecular hydrogen bonding plays a key role in the construction of the tetracyclic acridone core. The strong intramolecular hydrogen bonding between the C5-OH group and the carbonyl moiety promotes the efficient and regioselective mono-annulation. We could obtain a product like **7** (Scheme 4) but not the pentacyclic acridone core **8**, as the C5-OH group does not participate in annulation due to this hydrogen bonding. The single-crystal X-ray analysis of compound **2b** also clearly demonstrates this hydrogen bonding (Figure 2, CCDC **2063223**; Figure S1, Supporting Information (S.I.)).[20]

Next, we planned to expand this synthetic route for the preparation of oxa and thia analogues of tetracyclic acridones. The condensation of salicylic acid and thiosalicylic acid (**9a** and **9b**, respectively) with phloroglucinol **6** generated the dihydroxy oxa and thia acridone derivatives **10a** and **10b** in excellent yields (Scheme 4).[21] The regioselective annulation of **10a** and **10b** under the developed reaction conditions furnished the desired oxa and thia tetracyclic acridone derivatives **11a** and **11b** in 73 and 70% yields, respectively (Scheme 5).

CONCLUSIONS

In conclusion, we have demonstrated a new and efficient synthetic route for the construction of different acridone alkaloids. The synthetic route is feasible, enabling the target compounds in excellent yields. Titanium isopropoxide-mediated intramolecular hydrogen bonding-directed regioselective mono-annulation is employed for the construction of the tetracyclic core of acridone natural products. Acronycine and noracronycine are synthesized in high overall yields than those already reported. Two new acridone alkaloids, atalaphyllidine and 5-hydroxynoracronycine, are successfully and efficiently synthesized. Moreover, we have extended this synthetic pathway for constructing tetracyclic oxa and thia acridone alkaloids.

EXPERIMENTAL SECTION

General Information. All experiments were carried out under an inert atmosphere of argon in flame-dried flasks. Solvents were dried using standard procedures. All starting materials were obtained from commercial suppliers and used as received. Products were purified by flash chromatography on silica gel (100−200 mesh, Merck). Unless otherwise stated, yields refer to analytical pure samples. NMR spectra were

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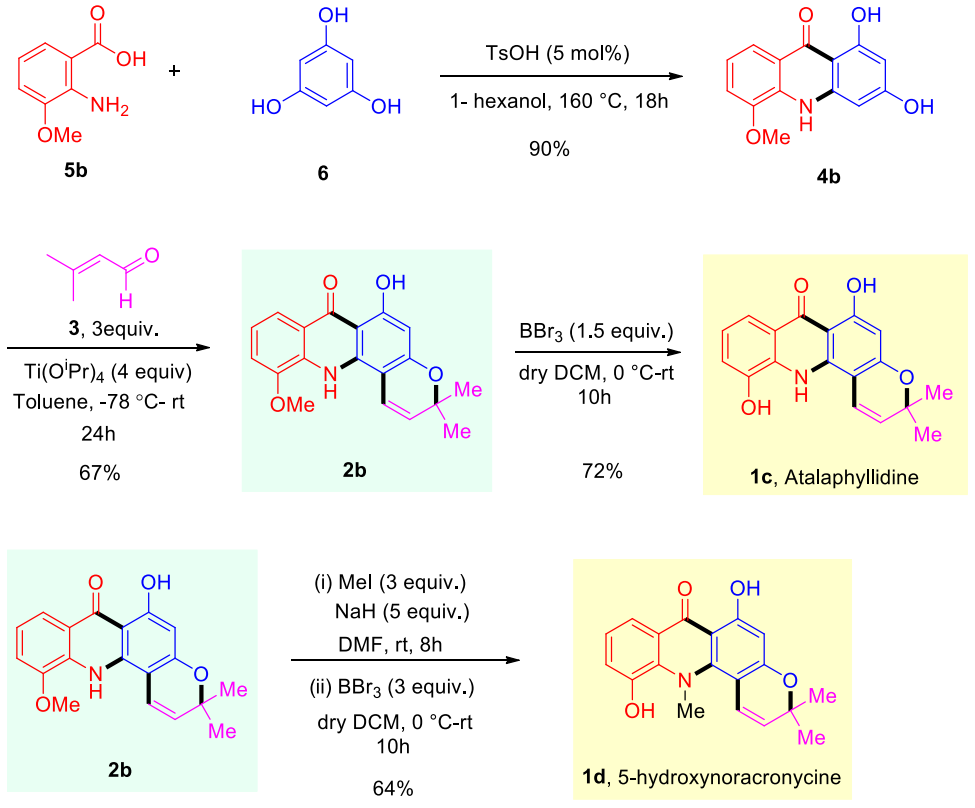
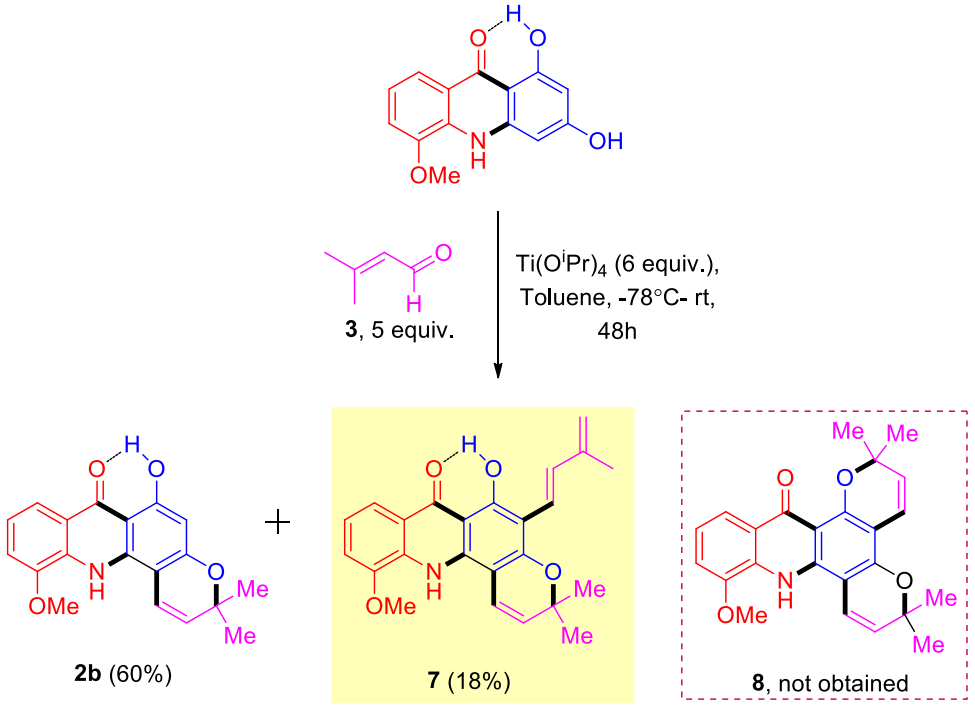
Scheme 3. Synthesis of Atalaphyllidine and 5-Hydroxynoracronycine



Scheme 4. Intramolecular Hydrogen Bonding-Directed Annulation



recorded in dimethyl sulfoxide (DMSO)-d_6 unless otherwise stated. **^{1}H NMR** spectra were recorded using Brüker AVANCE 500 MHz and JEOL-400 MHz instruments at 298K. Signals are quoted as δ values in ppm using the residual protonated solvent signal as internal standard (DMSO-d_6: δ 2.50 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), and coupling constants (Hz). **^{13}C NMR** spectra were recorded on either a JEOL-400 (100 MHz) or a Brüker ADVANCE 500 MHz (125 MHz) with complete proton decoupling. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane with the

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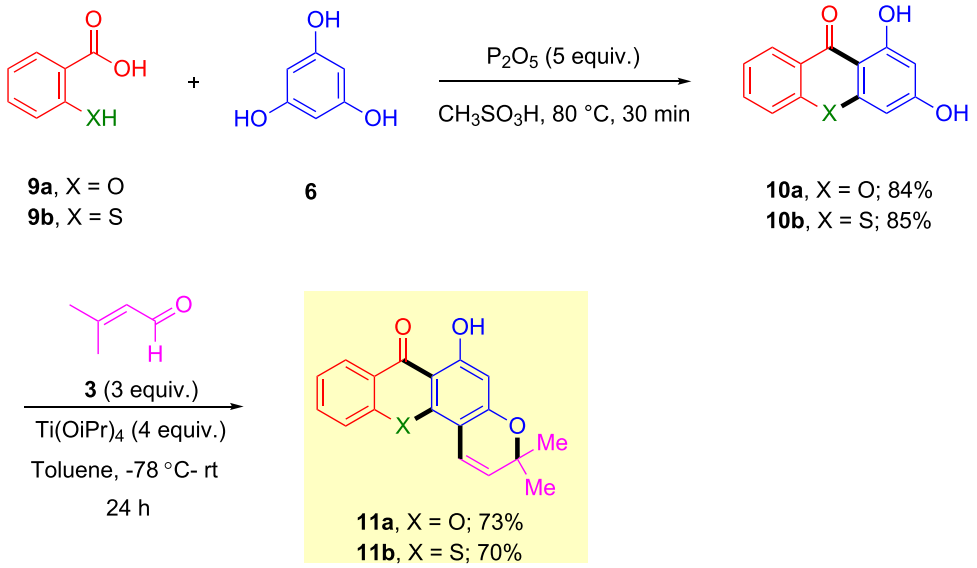
Scheme 5. Synthesis of Oxa and Thia Analogues of Acronycine



solvent as the internal reference (DMSO-d_6: δ 39.50 ppm). High-resolution mass spectrometry (**HRMS**) analyses were performed with Q-TOF YA263 high-resolution (Water Corporation) instruments by +ve mode electrospray ionization.

General Procedure for the Synthesis of the Tricyclic Acridone Derivative (GP-1). To a solution of anthranilic acid derivative **5** (1.0 equiv) and phloroglucinol **6** (1.0 equiv) in 1-hexanol, *p*-toluenesulfonic acid (TsOH, 0.05 equiv) was added and the reaction mixture was refluxed at 160 °C for 18 h. After 30 min, the color of the homogeneous solution became deep orange and after the reaction was over, a greenish yellow precipitate was formed. After cooling the reaction mixture to room temperature, *n*-hexane was added. The resulting precipitate was filtered and washed with hexane and dichloromethane until the odor of 1-hexanol diminished. Finally, the residue was dried in vacuum to provide the 1,3-dihydroxyacridone derivative **4**, which was used directly for the next step without further purification (Scheme S1, S.I.).

Synthesis of 1,3-Dihydroxyxanthone and 1,3-Dihydroxythioxanthone (GP-2). A mixture of phosphorus pentoxide (5 equiv) and methanesulfonic acid (25 mL) was heated on a steam bath (80 °C) for 15 min until a clear solution was obtained. To this solution, phloroglucinol (1.0 equiv) and the corresponding heteroaromatic benzoic acid (1.0 equiv) were added and the reaction mixture was allowed to stir for 15 min at this temperature. After completion of the reaction, the mixture was poured into ice-cold water and formation of the precipitate was observed. The resulting precipitate was collected by filtration, washed with water, and dried in air to afford acridone derivative **10** (Scheme S2, S.I.).

General Procedure for Ti(O^{i}Pr)$_4$-Mediated Regioselective Cyclization (GP-3). To a stirred solution of dihydroxyacridone derivatives **4** and **10** (1.0 equiv) and prenal **3** (3.0 equiv) in dry toluene at −78 °C was added Ti(O^{i}Pr)$_4$ (4.0 equiv) dropwise. The reaction mixture was allowed to stir vigorously for 24 h. After completion of the reaction as monitored by thin layer chromatography (TLC), the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was then purified by column chromatography on silica gel with EtOAc-hexane to give compounds **2** and **11** (Scheme S3, S.I.).

Synthesis of Acronycine 1a. To a solution of **2a** (1.0 equiv, 3.21 mmol) in dimethylformamide (DMF) was added NaH (3 equiv, 10.23 mmol) portionwise at 0 °C, and the reaction mixture was allowed to stir at 0 °C for 30 min. After that, MeI (3 equiv, 10.23 mmol) was added to the reaction mixture and the reaction was allowed to stir at room temperature for 8 h. After completion of the reaction as monitored by TLC, the reaction was quenched with addition of ice-cold saturated ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, and the solvent was removed under reduced pressure. It was then purified by column chromatography on silica gel with EtOAc-hexane to provide acronycine (967 mg, 90%) **1a** as a greenish yellow solid.

Synthesis of Noracronycine 1b. To a solution of **1a** (1.0 equiv, 3.11 mmol) in dichloromethane was added BBr_3 (1.5 equiv, 1 M in DCM) dropwise at 0 °C, and the reaction mixture was allowed to stir for 10 h at room temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was then purified by column chromatography on silica gel with EtOAc-hexane to give the target demethylated product noracronycine **1b** (745 mg, 78%) as a greenish yellow solid.

Synthesis of Atalaphyllidine 1c. To a solution of **2b** (1.0 equiv, 3.09 mmol) in dichloromethane was added BBr_3 (1.5 equiv, 1 M in DCM) dropwise at 0 °C, and the reaction mixture was allowed to stir for 10 h at room temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was then purified by column chromatography on silica gel with EtOAc-hexane to provide atalaphyllidine **1c** (688 mg, 72%) as a greenish yellow solid.

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Synthesis of 5-Hydroxynoracronycine 1d. To a solution of compound **2b** (1.0 g, 3.09 mmol) in DMF was added NaH (3 equiv, 9.27 mmol) portionwise at 0 °C, and the reaction mixture was allowed to stir at 0 °C for 30 min. After that, MeI (3 equiv, 9.27 mmol) was added to the reaction mixture and the reaction was allowed to stir at room temperature for 8 h. After completion of the reaction as monitored by TLC, the reaction was quenched with addition of ice-cold saturated ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, and the solvent was removed under reduced pressure to obtain the crude dimethylated intermediate. The crude compound was then directly taken in dichloromethane, BBr_3 (1.5 equiv, 1 M in DCM) was added dropwise at 0 °C, and the reaction mixture was allowed to stir for 10 h at room temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was then purified by column chromatography on silica gel with EtOAc-hexane to provide 5-hydroxynoracronycine **1d** (639 mg, 64%) as a greenish yellow solid.

Analytical Data of Compounds. *1,3-Dihydroxyacridinone (**4a**).*[13] Using the general procedure **GP-1**, anthranilic acid **5a** (2.0 g, 14.59 mmol) and phloroglucinol **6** (1.84 g, 14.59 mmol) were used to provide compound **4a** (2.91 g, 88%) as a yellowish green amorphous powder. m.p.: 344−346 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 14.23 (1H, s), 11.77 (1H, s), 10.52 (1H, s), 8.14 (1H, d, J = 8.4 Hz), 7.70 (1H, t, J = 7.6 Hz), 7.46 (1H, d, J = 8.4 Hz), 7.24 (1H, t, J = 6.7 Hz), 6.30 (1H, s), 6.00 (1H, s); ^{13}C (100 MHz, DMSO-d_6): 180.0, 164.2, 163.7, 143.3, 140.7, 133.7, 125.0, 121.1, 118.8, 116.8, 103.2, 95.6, 90.8; HRMS (ESI) calcd for $C_{13}H_{10}NO_3$ [M + H]$^+$: 228.0661; Found: 228.0657.

*1,3-Dihydroxy-5-methoxyacridinone (**4b**).*[13] Using the general procedure **GP-1**, 3-methoxy anthranilic acid **5b** (2.0 g, 11.97 mmol) and phloroglucinol **6** (1.5 g, 11.97 mmol) were used to provide compound **4b** (2.76 g, 90%) as a yellowish green amorphous powder. m.p.: 350−352 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 14.26 (1H, s_{br}), 11.23 (1H, s), 10.45 (1H, s_{br}), 7.71 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 8.0 Hz), 7.17 (1H, t, J = 8.0 Hz), 6.68 (1H, s), 6.00 (1H, s), 4.01 (3H, s); ^{13}C (100 MHz, DMSO-d_6): 179.8, 163.9, 163.4, 147.3, 143.1, 131.7, 120.7, 119.4, 116.1, 112.7, 103.4, 95.8, 92.0, 56.2; HRMS (ESI) calcd for $C_{14}H_{12}NO_4$ [M + H]$^+$: 258.0766; Found: 258.0764.

*1,3-Dihydroxyxanthone (**10a**).*[21] Using the procedure **GP-2**, salicylic acid **9a** (2.0 g, 14.49 mmol) and phloroglucinol **6** (1.82 mg, 14.49 mmol) were used to provide compound **10a** (2.77 g, 84%) as a reddish brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): 12.87 (1H, s_{br}), 11.12 (1H, s_{br}), 8.14 (1H, d, J = 8.1 Hz), 7.86 (1H, t, J = 7.9 Hz), 7.60 (1H, d, J = 8.5 Hz), 7.47 (1H, t, J = 7.4 Hz), 6.41 (1H, s), 6.22 (1H, s); ^{13}C (100 MHz, DMSO-d_6): 179.7, 165.9, 162.8, 157.4, 155.3, 135.6, 125.2, 124.4, 119.8, 117.7, 102.2, 98.1, 94.0; HRMS (ESI) calcd for $C_{13}H_9O_4$ [M + H]$^+$: 229.0501; Found: 229.0093.

*1,3-Dihydroxythioxanthone (**10b**).*[21] Using the procedure **GP-2**, 2-mercaptobenzoic acid **9b** (2.0 g, 12.98 mmol) and phloroglucinol **6** (1.63 g, 12.98 mmol) were used to provide compound **10b** (2.69 g, 85%) as a deep red solid. ^{1}H NMR (400 MHz, DMSO-d_6): 14.37 (1H, s), 11.08 (1H, s_{br}), 8.43 (1H, d, J = 7.9 Hz), 7.77−7.75 (2H, m), 7.59−7.55 (1H, m), 6.65 (1H, d, J = 2.2 Hz), 6.31 (1H, d, J = 2.2 Hz); ^{13}C (100 MHz, DMSO-d_6): 183.1, 166.6, 163.9, 140.0, 136.3, 133.2, 128.4, 127.3, 126.7, 125.8, 107.5, 103.0, 101.0; HRMS (ESI) calcd for $C_{13}H_9SO_3$ [M + H]$^+$: 245.0272; Found: 245.0269.

*6-Hydroxy-3,3-dimethyl-3H-pyrano[2,3-c]acridin-7(12H)-one (**2a**).*[15] Using the general procedure **GP-3**, 1,3-dihydroxyacridinone **4a** (2.0 g, 8.81 mmol), prenal **3** (2.5 mL, 26.43 mmol), and Ti(O^{i}Pr)$_4$ (10.4 mL, 35.24 mmol) were used to yield compound **2a** (1.8 g, 70%) as a greenish yellow solid. m.p.: 216−218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 14.65 (1H, s), 11.15 (1H, s), 8.16 (1H, d, J = 8.7 Hz), 7.80−7.73 (2H, m), 7.32−7.28 (1H, m), 7.00 (1H, d, J = 9.9 Hz), 6.04 (1H, s), 5.73 (1H, d, J = 10.0 Hz), 1.43 (6H, s); ^{13}C (100 MHz, DMSO-d_6): 180.5, 163.8, 159.2, 140.8, 137.7, 133.9, 125.7, 124.8, 121.8, 118.8, 117.5, 116.0, 103.9, 98.0, 96.2, 77.0, 27.4; HRMS (ESI) calcd for $C_{18}H_{16}NO_3$ [M + H]$^+$: 294.1130; Found: 294.1127.

*6-Hydroxy-11-methoxy-3,3-dimethyl-3H-pyrano[2,3-c]-acridin-7(12H)-one (**2b**).* Using the general procedure **GP-3**, 1,3-dihydroxy-5-methoxyacridinone **4b** (2.0 g, 7.78 mmol), prenal **3** (2.3 mL, 23.3 mmol), and Ti(O^{i}Pr)$_4$ (9.21 mL, 31.12 mmol) were used to yield compound **2b** (1.68 g, 67%) as a greenish yellow amorphous solid. m.p.: 200−202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 14.53 (1H, s), 9.71 (1H, s), 7.73 (1H, dd, J = 8.1 Hz, 1.1 Hz), 7.37 (1H, dd, J = 7.8 Hz, 1.0 Hz), 7.25 (1H, t, J = 8.0 Hz), 7.00 (1H, d, J = 10.0 Hz), 6.07 (1H, s), 5.70 (1H, d, J = 10.0 Hz), 4.02 (3H, s), 1.42 (6H, s); ^{13}C (125 MHz, DMSO-d_6): 180.5, 163.3, 159.1, 147.3, 136.8, 131.2, 125.6, 121.7, 119.5, 115.9, 115.8, 113.2, 104.1, 98.3, 96.5, 77.1, 56.3, 27.4HRMS (ESI) calcd for $C_{19}H_{18}NO_4$ [M + H]$^+$: 324.1236; Found: 324.1232.

*6-Hydroxy-3,3-dimethylpyrano[2,3-c]xanthen-7(3H)-one (**11a**).* Using the general procedure **GP-3**, 1,3-dihydroxyxanthone **10a** (2.0 g, 8.77 mmol), prenal **3** (2.51 mL, 26.31 mmol), and Ti(O^{i}Pr)$_4$ (10.38 mL, 35.08 mmol) were used to yield compound **11a** (1.88 g, 73%) as a deep red solid. m.p.: 176−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 12.96 (1H, s), 8.25 (1H, d, J = 7.9 Hz), 7.71 (1H, t, J = 7.7 Hz), 7.46 (1H, d, J = 8.4 Hz), 7.38 (1H, t, J = 7.5 Hz), 6.84 (1H, d, J = 10.0 Hz), 6.27 (1H, s), 5.61 (1H, d, J = 10.0 Hz), 1.49 (6H, s); ^{13}C (100 MHz, $CDCl_3$): 181.0, 163.4, 161.1, 156.0, 151.9, 135.0, 127.3, 126.1, 124.2, 120.8, 117.7, 115.1, 103.9, 101.2, 99.5, 78.4, 28.4; HRMS (ESI) calcd for $C_{18}H_{15}O_4$ [M + H]$^+$: 295.0970; Found: 295.0966.

*6-Hydroxy-3,3-dimethylthiochromeno[2,3-f]chromen-7(3H)-one (**11b**).* Using the general procedure **GP-3**, 1,3-dihydroxythioxanthone **10b** (2.0 g, 8.19 mmol), prenal **3** (2.35 mL, 24.59 mmol), and Ti(O^{i}Pr)$_4$ (9.69 mL, 32.76 mmol) were used to yield compound **11b** (1.77 g, 70%) as a deep red solid. m.p.: 234−236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 14.71 (1H, s), 8.55 (1H, d, J = 8.0 Hz), 7.61 (1H, t, J = 8.1 Hz), 7.55 (1H, d, J = 7.9 Hz), 7.47 (1H, t, J = 8.1 Hz), 6.63 (1H, d, J = 10.0 Hz), 6.39 (1H, s), 5.70 (1H, d, J = 10.0 Hz), 1.43 (6H, s); ^{13}C (100 MHz, $CDCl_3$): 132.6, 129.3, 128.4, 128.2, 126.3, 125.5, 116.0, 103.4, 78.3, 28.6; HRMS (ESI) calcd for $C_{18}H_{15}SO_3$ [M + H]$^+$: 311.0742; Found: 311.0741.

*Acronycine **1a**.*[15] m.p.: 176−178 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 8.08 (1H, dd, J = 1.9, 6.3 Hz), 7.72−7.69 (1H, m), 7.54 (1H, d, J = 8.2 Hz), 7.26 (1H, t, J = 7.6 Hz), 6.68 (1H, d, J = 9.5 Hz), 6.38 (1H, s), 5.61 (1H, d, J = 10.1 Hz), 3.83 (3H, s), 3.79 (3H, s), 1.49 (6H, s); ^{13}C (100 MHz, DMSO-d_6): 175.3, 162.1, 158.6, 146.1, 144.1, 132.7, 125.8, 124.6, 123.0, 121.5, 117.0, 109.6, 102.7, 94.1, 76.2, 55.9, 43.9,

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26.4; HRMS (ESI) calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$: 322.1443; Found: 322.1436.

Noracronycine **1b**.[15] m.p.: 200−202 °C; 1H NMR (400 MHz, DMSO-d_6): 14.86 (1H, s), 8.24 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.90−7.85 (1H, m), 7.71 (1H, d J = 8.6 Hz), 7.40 (1H, t, J = 7.4 Hz), 6.77 (1H, d, J = 9.6 Hz), 6.16 (1H, s), 5.63 (1H, d, J = 9.6 Hz), 3.93 (3H, s), 1.49 (6H, s); 13C (100 MHz, DMSO-d_6): 180.3, 164.2, 160.9, 144.5, 143.9, 134.5, 125.1, 122.9, 122.3, 121.3, 120.8, 117.4, 101.0, 96.6, 76.5, 43.4, 26.5; HRMS (ESI) calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$: 308.1287; Found: 308.1294.

Atalaphyllidine **1c**. m.p.: 274−276 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 14.64 (1H, s), 10.86 (1H, s_{br}), 9.62 (1H, s_{br}), 7.63 (1H, d, J = 8.0 Hz), 7.20 (1H, dd, J = 1.4, 7.6 Hz), 7.15 (1H, t, J = 7.8 Hz), 7.00 (1H, d, J = 10.0 Hz), 6.06 (1H, s), 5.70 (1H, d, J = 10.0 Hz), 1.43 (6H, s); ^{13}C (100 MHz, DMSO-d_6): 180.7, 163.6, 159.1, 145.3, 136.8, 130.8, 125.7, 121.9, 119.9, 116.8, 115.6, 114.8, 103.9, 98.1, 96.3, 77.1, 27.4; HRMS (ESI) calcd for $C_{18}H_{16}NO_4$ $[M + H]^+$: 310.1079; Found: 310.1078.

5-Hydroxynoracronycine **1d**. m.p.: 252−254 °C; 1H NMR (400 MHz, DMSO-d_6): 14.43 (1H, s), 7.94 (1H, d, J = 7.4 Hz), 7.17−7.09 (3H, m), 6.66 (1H, d, J = 9.3 Hz), 5.84 (1H, s_{br}), 5.55 (1H, d, J = 9.8 Hz), 3.75 (3H, s), 1.52 (6H, s); 13C (100 MHz, DMSO-d_6): 182.0, 161.9, 159.6, 146.6, 123.9, 123.1, 121.4, 121.0, 120.0, 118.6, 107.0, 106.8, 102.3, 98.5, 48.7, 27.; HRMS (ESI) calcd for $C_{19}H_{18}NO_4$ $[M + H]^+$: 324.1236; Found: 324.1237.

(E)-6-Hydroxy-11-methoxy-3,3-dimethyl-5-(3-methylbuta-1,3-dien-1-yl)-12,12a-dihydro-3H-pyrano[2,3-c]acridin-7-(6aH)-one (**7**). Obtained as a yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6): 14.85 (1H, s), 9.44 (1H, s), 7.71 (1H, d, J = 6.5 Hz), 7.36 (1H, d, J = 6.1 Hz), 7.25 (1H, t, J = 6.4 Hz), 6.92 (1H, d, J = 13.4 Hz), 6.65−6.60 (2H, m), 5.74 (1H, d, J = 7.9 Hz), 5.16 (2H, s), 4.00 (3H, s), 2.03 (2H, s), 1.45 (6H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 180.7, 157.1, 156.3, 146.8, 141.7, 137.8, 134.5, 130.5, 127.2, 121.8, 119.1, 119.0, 117.2, 116.0, 115.0, 113.0, 103.6, 101.6, 101.4, 78.0, 56.7, 27.9, 18.0; HRMS (ESI) calcd for $C_{24}H_{24}NO_4$ $[M + H]^+$: 390.1705; Found: 390.1703.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03629.

Synthesis of tricyclic acridone derivatives, Synthesis of 1,3-dihydroxyxanthone and 1,3-dihydroxythioxanthone, Ti(O^iPr)$_4$-mediated regioselective annulation, X-ray crystal data of compound **2b**, The copies of ^{1}H NMR and ^{13}C NMR (PDF)

Compound **2b** (CIF)

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Notes

The authors declare no competing financial interest.

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