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Setbacks and hopes: en route to the synthesis of uncialamycin

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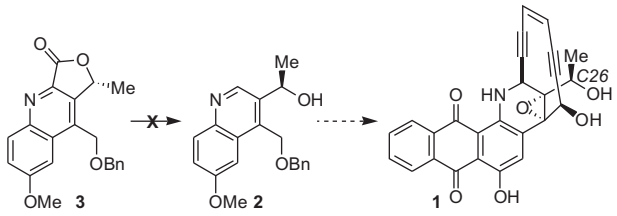
ABSTRACT

We herein report a new approach toward the synthesis of uncialamycin, an enediyne natural product isolated from the *Streptomyces uncialis*, bacteria present on the surface of the lichen *Cladonia uncialis*. A model for the preparation of uncialamycin has been achieved through a reaction cascade, an acetylide addition to the activated quinoline moiety, and a ring closure reaction as key steps.

1. Introduction

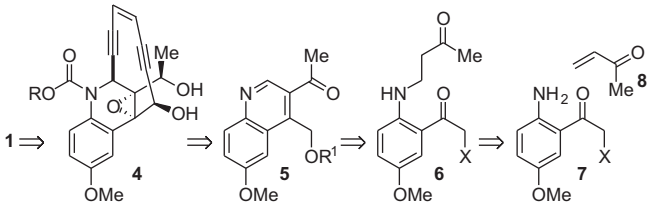
In 2005, Davies, Andersen and co-workers disclosed the uncialamycin **1**, a new enediyne natural product isolated from an undescribed streptomycete obtained from the surface of the lichen *Cladonia uncialis*.[1] First biological evaluations show that **1** possesses potent in vitro antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Burkholderia cepacia*. Despite of the small amount of product available, the structure of **1** was resolved but assigning the absolute configuration of C26 was not possible. Nicolaou and co-workers recently proved without ambiguity the complete structure of **1** and determined the absolute stereochemistry at C26 after total synthesis of the racemic and then reported the first asymmetric synthesis.[2] Having ample quantities of **1** and its C26-epimer in hand, they studied its biological properties in DNA-cleavage, antibacterial, and cytotoxic activities. These investigations revealed impressive high potent antitumor activities and broad-spectrum antibacterial properties.

While Nicolaou reported an approach using a Friedländer quinoline synthesis, we developed an intramolecular imino-Diels–Alder reaction promoted with $BF_3{\cdot}OEt_2$/DDQ to synthesize the chiral quinoline core **3**.[3] To prepare the intermediate **2**, suitable for the introduction of the enediyne moiety, we planned to accomplish first a lactone opening reaction followed by a decarboxylation. Despite several attempts, we never succeeded in this way (Scheme 1). Therefore, our first strategy has been completely reconsidered in order to prepare an advanced intermediate of uncialamycin **1**.



Scheme 1.

Based on the results reported by Hamada and co-workers concerning a Michael-aldolisation–crotonisation reaction cascade to prepare the quinoline core of the martinelline in good yield,[4] we planned to prepare our quinoline skeleton by using a similar approach. The retrosynthesis of the intermediate **4** is depicted in Scheme 2. This strategy relied on three key steps: a Sugasawa reaction[5] to prepare **7**, a Michael addition with methyl vinyl ketone **8** following by an aldol-crotonisation sequence to afford the quinoline **5**.



Scheme 2.

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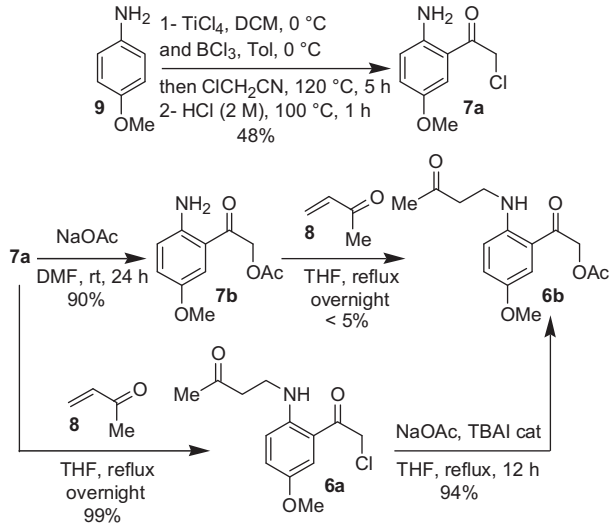
2. Results and discussion

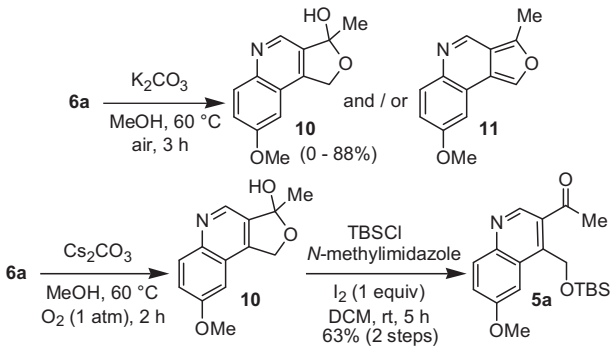
2.1. Construction of the quinoline moiety

Our first task was to prepare the aniline derivative **7a** (X=Cl) from *p*-anisidine **9** (Scheme 3). Using the Sugasawa reaction conditions as reported by Prasad,[5c] an *ortho*-acylation of **9** by condensation of chloroacetonitrile in the presence of $TiCl_4/BCl_3$ with a substantial HCl expulsion, **7a** has been obtained in satisfactory yield (48%). Then **7a** has been treated in the presence of NaOAc in DMF to furnish the acetate **7b** in good yield. Surprisingly **7b** did not react with an excess of methyl vinyl ketone **8**. However, **6b** was obtained efficiently by simple reversing order of the last two steps (Scheme 3).



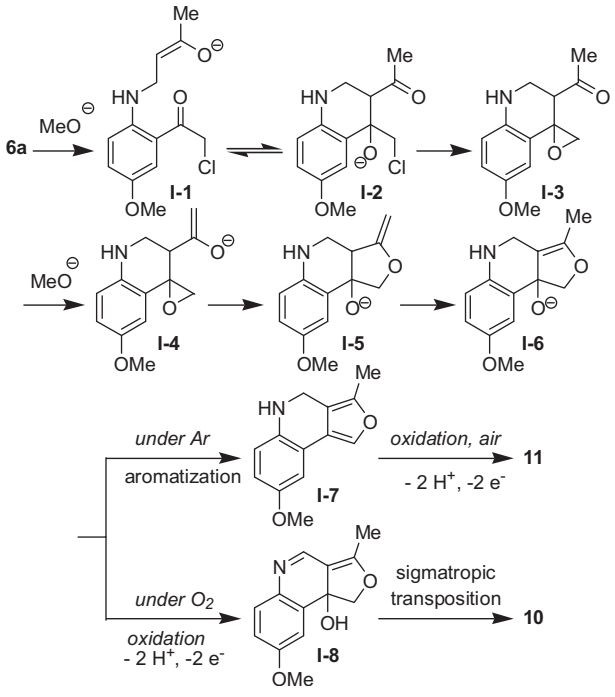
Scheme 3.

To build the quinoline core, the Michael adduct **6b** was submitted to basic treatment (K_2CO_3/MeOH, LDA/THF, DBU/THF and *t*-BuOK/THF). Whatever the reaction conditions employed, no expected product was obtained and only a complex mixture of degradation products was observed. On the other hand, submitting **6a** to K_2CO_3 in methanol under air at 60 °C led to the hemiketal **10** along with furan **11** as side product in variable ratio **10**/**11**. After careful examination of the reaction conditions, the chloride **6a** has been successfully converted to the expected hemiketal **10** after stirring 2 h at 60 °C in methanol in the presence of Cs_2CO_3 under an oxygen atmosphere. After the reaction of the hemiketal **10** with TBSCl, *N*-methylimidazole, and I_2 in methylene chloride,[6] the ketone **5a** was isolated in 63% yield over two steps (Scheme 4).



Scheme 4.

To understand the mechanism of the process of the formation of the quinoline moiety, **6a** has been placed in the presence of K_2CO_3 in methanol under an argon atmosphere. After 3 h under reflux, the methanol was directly evaporated and the crude reaction mixture rapidly analyzed by NMR. Only the compound **I-7** was observed, and after 2–3 h exposure to air atmosphere it was completely converted to the furan **11** (Scheme 5). An attempt to explain the formation of hemiketal **10** and/or furan **11** from **6a** is proposed. After formation of the enolate **I-1**, an aldolization could lead to the tetrahydroquinoline **I-3**, which could provide a postulated dihydrofuran **I-6** by nucleophilic substitution of the chloride and double bond migration. From the key intermediate **I-6** and depending of the atmospheric reaction conditions, a loss of hydroxide could give **I-7** under an inert atmosphere followed by an oxidation of this tetahydroquinoline leading to the furan **11**. The structure of **I-7** was confirmed after isolation of *N*-acyl **I-7** by exposure of the crude reaction mixture from **6a** and K_2CO_3 in dry methanol to acetic anhydride in pyridine. On the other hand, under an oxygen atmosphere, first **I-6** would be oxidized in dihydroquinoline **I-8** followed by a sigmatropic transposition of the hydroxyl group favored by the aromatization of the heterocycle to yield the expected product **10**.

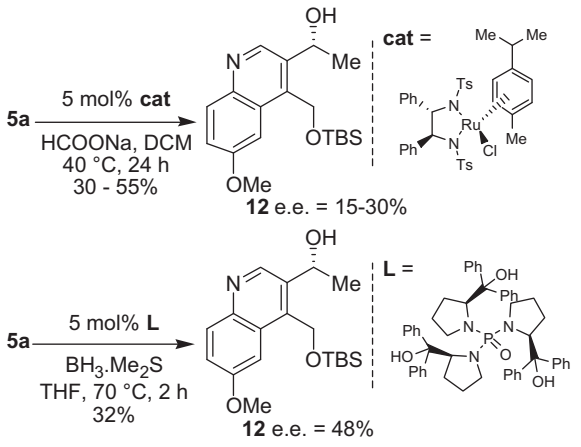


Scheme 5.

Having the ketone **5a** in hand, its enantioselective reduction has been undertaken by using different methods. Among the numerous reductive process studied, best results were obtained either under the Noyori reduction conditions[7] or using a borane reduction in the presence of the chiral phosphoramide derivative **L**.[8] Unfortunately the yield and the enantiomeric excess of the alcohol **12** are too low to continue the synthesis under its asymmetric form. In parallel, we decided to carry on our progress toward the preparation of a valuable intermediate with the racemic alcohol **12** obtained after treatment of **5a** with $NaBH_4$ in methanol (Scheme 6).

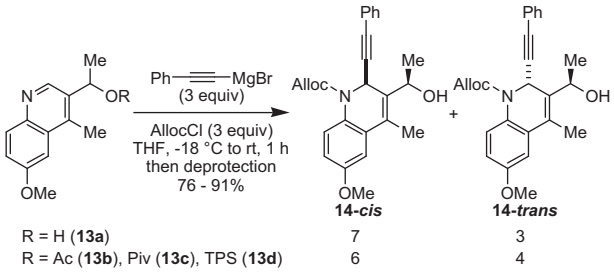
2.2. Preliminary studies of enediyne addition

Using a model,[9] we then examined the influence of the protection of the secondary alcohol onto the diastereoselectivity in the



Scheme 6.

Reissert-type step reaction. Compounds **13a**–**d** were submitted to phenylacetylene magnesium bromide with allyloxycarbonyl chloride as activating agent (Scheme 7). Whatever the protecting group used, a moderate diastereomeric excess in favor of the cis-isomer was observed, the relative configurations being confirmed by X-ray analysis of **14**-*cis* (Fig. 1).



Scheme 7.

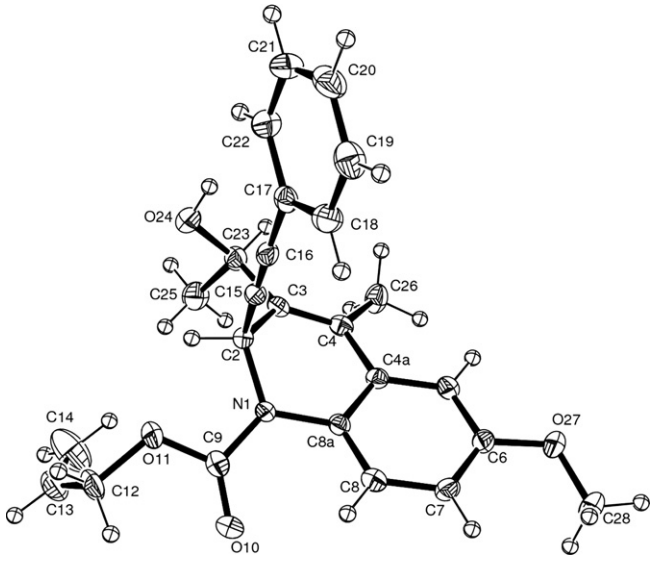
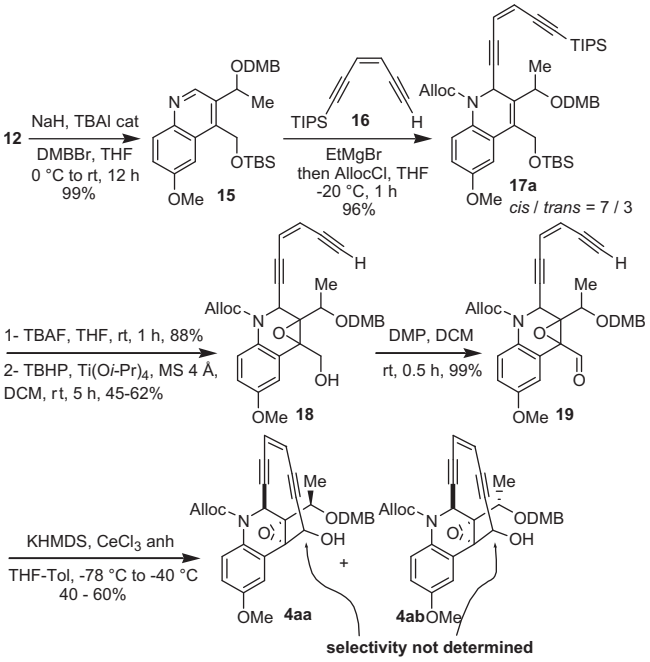


Fig. 1. X-ray structure of **14**-*cis*.

2.3. En route to the synthesis of uncialamycin

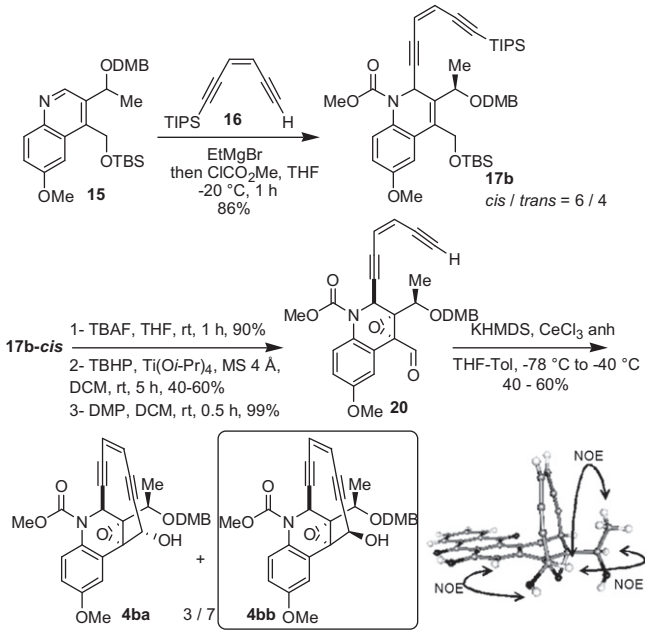
Because the best selectivity has been obtained with the quinoline model **13a**, the alcohol **12** was first submitted to the Reissert-type addition in the presence of the Grignard reagent prepared in situ from the enediyne **16**[10] and an excess of allyloxycarbonyl chloride. The two diastereoisomers were not separable and were isolated in 86% yield in a 7:3 ratio. In attempt to improve the efficiency of the reaction, we decided to start with the protection of the secondary alcohol of **12** as a 3,4-dimethoxybenzylether (DMB). This protecting group leaving under oxidative conditions, we postulated that it could be removed in the oxidative step of the aromatic ring to the iminoquinone which is required to build the anthraquinone core of **1** through a Hauser annulation. The activation of the nitrogen of the quinoline core **15** with allyloxycarbonyl chloride and reaction with the corresponding enediyne **16** Grignard derivative afforded the expected compound **17a** isolated in good yield albeit as an inextricable mixture of diastereoisomers in the same ratio as previously. Consequently **17a** was used as the cis/trans isomers mixture to prepare the aldehyde **19** in three steps. After removal of the silyl groups of **17a** with TBAF, the product was then regioselectively oxidized with TBHP/Ti(O*i*-Pr)$_4$ to afford a non-separable mixture of isomers **18** in modest yield. In the presence of an excess of the Dess–Martin periodinane, the alcohol was converted quantitatively to its aldehyde **19**. Once again it was not possible to separate each stereoisomer, and thus to characterize them suitably to identify the one who possesses the stereochemical relationship corresponding to the pattern of the uncialamycin **1**. Exposure of the mixture of stereoisomers **19** to KHMDS in the presence of anhydrous $CeCl_3$ afforded the 10-membered ring enediyne as a complex mixture of isomers **4aa** and **4ab** in low yield. In spite of our efforts, we were not able to separate each isomer during the purification and thus in the impossibility to determine the selectivity of this crucial cyclization step (Scheme 8).



Scheme 8.

Facing these difficulties of isomers separation and in order to facilitate the characterization of each product by NMR, we changed the agent of activation of the quinoline **15** by using the methyl chloroformate (Scheme 9).[11] The addition of the Grignard reagent of the enediyne **16** was achieved to furnish **17b** in good yield as a mixture of cis/trans isomers in an unchanged ratio 6:4. The stereoisomers were separated by flash chromatography.[12] Each of these isomers were then submitted to the 2-steps sequence

deprotection–epoxidation and while the isomer **17b**-*cis* led to a single isomer of the corresponding oxirane, the trans-isomer gave a complex mixture of compounds. This result led us to continue only with the epoxide obtained from the isomer **17b**-*cis*. After oxidation of the primary alcohol, the cyclization step was carried out using KHMDS in the presence of anhydrous $CeCl_3$ and afforded a mixture of **4bb** and **4ba** in a ratio 7:3. The major product **4bb** was isolated and fully characterized. We were very pleased that the NMR spectroscopic data of **4bb** are consistent with the structure of the quinoline/enediyne moiety of the uncialamycin **1**.[13]



Scheme 9.

3. Conclusions

In conclusion, the synthesis of the valuable synthon **4bb** as model for the preparation of uncialamycin **1** has been achieved through a Michael-aldolisation–crotonisation reaction cascade, an acetylide addition to the activated quinoline moiety, and a ring closure reaction as key steps. Using methyl chloroformate as activating agent in the Reissert-type step allowed us to confirm that the major stereoisomer is consistent with the uncialamycin **1**. As reported by Sierra and de la Torre,[14] the work described in this article shows the failures in the planned synthetic scheme and also the difficulties to obtain some synthetic intermediates with high selectivities in spite of the use of well-established methods. Recognizing that the methyl carbamate protective group would be difficult to remove, our approach will be modified in order to solve the problem of isolation of the right isomer. More experimental efforts must also be dedicated to succeed in the enantioselective reduction of the ketone **5a**.

4. Experimental

4.1. General methods

All reagents and solvents were used as purchased from commercial suppliers or were purified/dried according to Armarego W. L. F. and Chai C. L. L. (Purification of Laboratory Chemicals, sixth edition, Elsevier.) ^1H and ^{13}C NMR spectra were recorded on a Bruker DMX 500, a Bruker Avance 300 or a Jeol JNM-GSX270 instrument using TMS and $CDCl_3$, respectively, as internal standard. δ values are given in parts per million (ppm), coupling constants (J values) are given in hertz (Hz), and multiplicity of signals are reported as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; m, multiplet. HRMS analyses were obtained using a Waters Q-TOF 2 or a Micromass ZABSpec TOF or a Bruker MicrO-TOF Q II instrument for ESI. X-ray structures were obtained using an Oxford Diffraction Xcalibur Saphir 3 diffractometer with graphite monochromatized MoK a radiation. Chiral HPLC was performed using a Daicel Chiralpak® AD-H column (5 μm, 4.6×250 mm). Melting points were uncorrected and obtained on a hot bench. TLC analyses were performed using precoated Merck TLC Silica Gel 60 F_{254} plates. Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (70–230 mesh) and purifications by preparative thin layer chromatography on silica gel using Merck Silica Gel 60 PF_{254}. Petroleum ether (PE) used for purifications was the low boiling point fraction (40–60 °C).

*4.1.1. 1-(2-Amino-5-methoxyphenyl)-2-chloroethanone (**7a**)*[5b]. To a solution of *p*-anisidine **9** (6.16 g, 50.0 mmol, 1 equiv) in dry CH_2Cl_2 (50 mL) was added at 0 °C titanium tetrachloride (5.45 mL, 50.0 mmol, 1 equiv), a solution of boron trichloride (1 M in PhMe, 55.0 mL, 55.0 mmol, 1.1 equiv) then chloroacetonitrile (15.2 mL, 240.0 mmol, 4.8 equiv) at room temperature. The resulting mixture was then heated at 120 °C for 5 h before being cooled down to room temperature and quenched with a 2 M aqueous solution of HCl (140 mL). The mixture was then heated at reflux for 1 h, cooled down to 0 °C, concentrated aqueous solution of NaOH was added until pH 4. The titanium salts were eliminated by filtration over a Celite pad and the product was extracted with EtOAc (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting dark residue was purified by column chromatography on silica gel using PE/EtOAc 9:1 as eluent affording **7a** as a yellow solid (4.79 g, **48**%). R_f=0.3 (cyclohexane/EtOAc 7:3). Mp=104–106 °C (lit. mp=103–104 °C). ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.65 (s, 2H), 6.02 (br s, 2H), 6.65 (d, J=9.0, 1H), 7.01 (dd, J=9.0, 3.0, 1H), 7.05 (d, J=3.0, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.6, 55.9, 112.6, 114.6, 118.9, 124.5, 146.0, 149.8, 191.9. HRMS (ESI) $[M+Na]^+$: calcd for $C_9H_{10}NO_2ClNa$ 222.0298, found 222.0303.

*4.1.2. 4-[2-(2-Chloroacetyl)-4-methoxyphenylamino]butan-2-one (**6a**).* To a solution of **7a** (2.10 g, 9.4 mmol, 1 equiv) in dry THF (40 mL) was added 3-buten-2-one **8** (1.53 mL, 18.8 mmol, 2 equiv). The mixture was heated at 65 °C in a sealed tube for 24 h then the solvent was evaporated under reduced pressure. After trituration of the brown residue in MeOH (10 mL) and filtration, the product **6a** was isolated as yellow solid (2.53 g, **99**%). R_f=0.2 (cyclohexane/EtOAc 7:3). Mp=130–132 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.81 (t, J=7.0, 2H), 3.49 (t, J=7.0, 2H), 3.78 (s, 3H), 4.65 (s, 2H), 6.75–6.77 (m, 1H), 7.10–7.12 (m, 2H), 8.52 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.3, 37.6, 42.8, 46.6, 56.1, 113.5, 114.0, 114.3, 124.9, 146.7, 148.9, 191.9, 206.6. HRMS (ESI) $[M+Na]^+$: calcd for $C_{13}H_{16}NO_3ClNa$ 292.0716, found 292.0714.

*4.1.3. 4-[2-(2-Acetyloxyacetyl)-4-methoxyphenylamino]butan-2-one (**6b**).* Sodium acetate (75 mg, 0.91 mmol, 1.2 equiv) and tetrabutylammonium iodide (25 mg, 0.07 mmol, 0.1 equiv) were added to a solution of **6a** (200 mg, 0.74 mmol, 1 equiv) in dry THF (5 mL). The reaction mixture was stirred overnight at reflux and was cooled down to room temperature before being quenched with water. The product was extracted with Et_2O (three times) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using PE/EtOAc 3:2 as eluent to give **6b** as a yellow oil (205 mg, **94**%). R_f=0.4 (cyclohexane/

EtOAc 1:1). Mp=96–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.24 (s, 3H), 2.79 (t, J=6.9, 2H), 3.48 (t, J=6.9, 2H), 3.77 (s, 3H), 5.29 (s, 2H), 6.74 (d, J=9.3, 1H), 7.04 (d, J=3.0, 1H), 7.10 (dd, J=9.3, 3.0, 1H), 8.38 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 30.4, 37.5, 43.0, 56.2, 65.7, 112.9, 113.3, 114.3, 124.6, 146.3, 148.9, 170.5, 192.7, 206.7. HRMS (ESI) $[M+Na]^+$: calcd for $C_{15}H_{19}NO_5Na$ 316.1161, found 316.1158.

*4.1.4. 8-Methoxy-3-methyl-1,3-dihydrofuro[3,4-c]quinolin-3-ol (**10**).* To a solution of **6a** (500 mg, 1.85 mmol, 1 equiv) in dry MeOH (10 mL) was added Cs_2CO_3 (1.81 g, 5.55 mmol, 3 equiv). The suspension was stirred at reflux under O_2 atmosphere for 3 h and a saturated aqueous solution of NH_4Cl was added. The product was extracted with EtOAc (four times) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The dark residue was purified by column chromatography on silica gel using cyclohexane/EtOAc 1:1 to 3:7 as eluent yielding to **10** as a pure beige solid (376 mg, **88**%). R_f=0.1 (cyclohexane/EtOAc 1:1). Mp=98–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (s, 3H), 3.83 (s, 3H), 5.12 (d, J=14.0, 1H), 5.23 (d, J=14.0, 1H), 5.89 (br s, 1H), 6.48 (d, J=3.0, 1H), 7.24 (dd, J=8.8, 3.0, 1H), 7.85 (d, J=8.8, 1H), 8.47 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 55.5, 69.5, 101.2, 108.5, 122.4, 123.3, 130.5, 134.9, 142.1, 143.0, 144.1, 158.1. HRMS (ESI) $[M+Na]^+$: calcd for $C_{13}H_{13}NO_3Na$ 254.0793, found 254.0798.

*4.1.5. 1-[4-(tert-Butyldimethylsilyloxymethyl)-6-methoxyquinolin-3-yl]ethanone (**5a**).* To a solution of *tert*-butyldimethylsilyl chloride (528 mg, 3.50 mmol, 1 equiv) and *N*-methylimidazole (840 μL, 10.50 mmol, 3 equiv) in dry CH_2Cl_2 (10 mL) at room temperature were added iodine (885 mg, 3.50 mmol, 1 equiv) and a solution of crude **10** (from 3.50 mmol of **6a**) in dry CH_2Cl_2 (10 mL). The mixture was stirred 5 h at room temperature and quenched with a saturated aqueous solution of $Na_2S_2O_5$. The product was extracted with Et_2O (three times) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting dark residue was purified by column chromatography on silica gel using cyclohexane/EtOAc 4:1 as eluent to afford **5a** as a brown solid (760 mg, **63**% over two steps). R_f=0.25 (cyclohexane/EtOAc 7:3). Mp=74–76 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.90 (s, 9H), 2.69 (s, 3H), 3.96 (s, 3H), 5.26 (s, 2H), 7.43 (dd, J=9.0, 2.7, 1H), 7.51 (d, J=2.7, 1H), 8.02 (d, J=9.0, 1H), 8.83 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, 18.3, 25.8, 31.3, 55.5, 58.9, 103.3, 123.3, 127.7, 131.3, 132.2, 142.7, 145.0, 145.6, 158.3, 202.2. HRMS (ESI) $[M+Na]^+$: calcd for $C_{19}H_{27}NO_3NaSi$ 368.1658, found 368.1658.

*4.1.6. 1-[4-(tert-Butyldimethylsilyloxymethyl)-6-methoxyquinolin-3-yl]ethanol (**12**).* Sodium borohydride (75 mg, 1.98 mmol, 1.05 equiv) was added by portion to a solution of **5a** (650 mg, 1.88 mmol, 1 equiv) in MeOH (10 mL) at 0 °C. After 15 min, water was added and the product was extracted with Et_2O (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow residue was purified by column chromatography on silica gel using cyclohexane/EtOAc 3:7 as eluent to obtain **12** as a pure beige solid (674 mg, **98**%). R_f=0.2 (cyclohexane/EtOAc 1:1). Mp=130–132 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 1.62 (d, J=6.6, 3H), 3.09 (br s, 1H), 3.93 (s, 3H), 5.10 (s, 2H), 5.41 (q, J=6.6, 1H), 7.32 (dd, J=8.8, 2.7, 1 H), 7.37 (d, J=2.7, 1 H), 7.96 (d, J=8.8, 1H), 8.88 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, −5.2, 18.3, 24.3, 25.8, 55.4, 57.2, 65.9, 102.2, 121.5, 127.7, 131.1, 136.0, 139.2, 143.7, 146.6, 158.0. HRMS (ESI) $[M+H]^+$: calcd for $C_{19}H_{30}NO_3Si$ 348.1989, found 348.1989.

*4.1.7. Allyl 3-(1-hydroxyethyl)-6-methoxy-4-methyl-2-(2-phenylethynyl)quinoline-1(2H)-carboxylate (**14**).* To a solution of phenylacetylene (198 μL, 1.80 mmol, 3 equiv) in anhydrous THF (2 mL) at 0 °C was added a solution of isopropylmagnesium chloride 2 M in THF (900 μL, 1.80 mmol, 3 equiv). After 2 h at room temperature, the reaction mixture was cooled to −18 °C then a solution of **13a** (130 mg, 0.60 mmol, 1 equiv) in THF (2 mL) and allyl chloroformate (191 μL, 1.80 mmol, 3 equiv) were added. The mixture was warmed to room temperature for 1 h and then treated with water. The product was extracted with EtOAc (three times) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The desired product was purified by column chromatography on silica gel using cyclohexane/EtOAc 9:1 as eluent to giving a mixture of two diastereoisomers A/B (7/3) as a yellow oil (244 mg, **83**%). R_f=0.4 (cyclohexane/EtOAc 7:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (d, J=6.5, 3H, A), 1.63 (d, J=6.5, 3H, B), 2.16 (s, 3H, A), 2.18 (s, 3H, B), 3.83 (s, 3H), 4.20 (dd, J=12.5, 6.0, 1H), 4.47 (dd, J=12.5, 6.0, 1H), 4.56–4.73 (m, 1H), 4.76 (dd, J=13.3, 5.5, 1H, B), 4.79 (dd, J=13.3, 5.5, 1H, A), 5.08 (d, J=10.5, 1H), 5.14 (d, J=17.0, 1H), 5.18–5.45 (m, 2H), 5.65–5.76 (m, 1H, A), 5.83–6.04 (m, 2H), 6.30 (br s, 1H), 6.79–6.89 (m, 1H), 6.91 (d, J=2.5, 1H, B), 6.95 (d, J=2.5, 1H, A), 7.13–7.25 (m, 5H), 7.90 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7 (A), 13.9 (B), 19.0 (B), 19.2 (A), 42.9 (A), 43.3 (B), 55.4 (A), 66.8 (B), 66.9 (A), 68.4 (B), 68.5 (A), 71.6 (B), 73.0 (A), 81.7 (A), 82.8 (B), 86.2 (A), 86.9 (B), 109.7 (A), 110.2 (B), 112.8, 117.9, 118.3, 118.8, 122.6, 125.6, 127.3, 127.9, 128.0, 128.1, 128.2, 130.7, 130.9, 131.3, 131.6, 131.9, 132.2, 132.3, 152.8, 154.0 (A), 154.2 (B), 156.5. HRMS (ESI) $[M+Na]^+$: calcd for $C_{29}H_{29}NO_6Na$ 510.1893, found 510.1902. To a solution of these two diastereoisomers (134 mg, 0.27 mmol, 1 equiv) in MeOH (2 mL) at room temperature was added potassium carbonate (4 mg, 0.03 mmol, 0.1 equiv) and the mixture was stirred overnight. Water was added and the product was extracted with EtOAc (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The two diastereoisomers (7/3) were separated by preparative TLC using cyclohexane/EtOAc 7:3 as eluent to obtain **14**-*cis* as a white solid (76 mg, **70**%) and **14**-*trans* as a yellow oil (32 mg, **30**%). Compound **14**-*cis*: R_f=0.20 (cyclohexane/EtOAc 7:3). Mp=105–107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, J=6.6, 3H), 1.93 (br s, 1H), 2.04 (s, 3H), 3.83 (s, 3H), 4.66 (br s, 1H), 4.79 (dd, J=13.2, 5.5, 1H), 5.08 (q, J=6.6, 1H), 5.16–5.44 (m, 2H), 5.90–6.05 (m, 1H), 6.25 (br s, 1H), 6.84 (dd, J=8.8, 1H), 6.92 (d, J=2.5, 1H), 7.09–7.25 (m, 5H), 7.56 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 21.5, 43.0, 55.5, 66.8, 82.0, 87.5, 109.5, 112.2, 118.1, 122.5, 125.0, 125.5, 127.5, 128.0, 128.2, 131.2, 131.8, 132.0, 132.3, 137.4, 152.9, 156.4. HRMS (ESI) $[M+Na]^+$: calcd for $C_{25}H_{25}NO_4Na$ 426.1681, found 426.1677. Compound **14**-*trans*: R_f=0.15 (cyclohexane/EtOAc 7:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (d, J=6.6, 3H), 1.88 (br s, 1H), 2.09 (s, 3H), 3.83 (s, 3H), 4.65 (br s, 1H), 4.77 (dd, J=13.2, 5.5, 1H), 5.03–5.10 (m, 1H), 5.22 (d, J=9.0, 1H), 5.25–5.43 (m, 1H), 5.89–6.04 (m, 1H), 6.41 (s, 1H), 6.81–6.85 (m, 1H), 6.88 (d, J=2.5, 1H), 7.14–7.25 (m, 5H), 7.57 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 21.6, 43.0, 55.5, 65.1, 82.7, 87.2, 110.0, 112.3, 117.9, 122.8, 125.7, 127.6, 128.0, 128.1, 128.2, 131.3, 131.6, 131.8, 132.3, 153.2, 156.4. HRMS (ESI) $[M+Na]^+$: calcd for $C_{25}H_{25}NO_4Na$ 426.1681, found 426.1677.

*4.1.8. 4-tert-Butyldimethylsilyloxymethyl-3-[1-(3,4-dimethoxybenzyloxy)ethyl]-6-methoxyquinoline (**15**).* To a solution of **12** (500 mg, 1.44 mmol, 1 equiv) in dry THF (10 mL) at 0 °C was added by portion sodium hydride 60% in mineral oil (86 mg, 2.16 mmol, 1.5 equiv). After 15 min at 0 °C, tetrabutylammonium iodide (106 mg, 0.29 mmol, 0.2 equiv) and 3,4-dimethoxybenzyl bromide (400 mg, 1.73 mmol, 1.2 equiv) were added. The suspension was warmed to room temperature overnight then the reaction was quenched with water. The product was extracted with Et_2O (three times) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using

cyclohexane/EtOAc 7:3 as eluent to give **15** as a yellow solid (702 mg, **98**%). R_f=0.25 (cyclohexane/EtOAc 3:2). Mp=74–76 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 1.60 (d, J=6.6, 3H), 3.86 (s, 3H), 3.87(s, 3H), 3.95(s, 3H), 4.27 (d, J=11.5, 1H), 4.43 (d, J=11.5, 1H), 5.06 (q, J=6.6, 1H), 4.98 (d, J=11.3, 1H), 5.15 (d, J=11.3, 1H), 6.81 (s, 2H), 6.86 (s, 1H), 7.36 (dd, J=9.0, 3.0, 1H), 7.44 (d, J=3.0, 1H), 8.03 (d, J=9.0, 1H), 8.96 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −5.3, 18.3, 24.1, 25.6, 25.8, 55.4, 55.8, 55.9, 57.0, 70.6, 72.3, 102.4, 110.9, 111.0, 120.3, 121.4, 127.9, 130.5, 131.0, 134.2, 140.0, 143.7, 147.2, 148.6, 149.0, 158.0. HRMS (ESI) $[M+Na]^+$: calcd for $C_{28}H_{39}NO_5NaSi$ 520.2490, found 520.2490.

*4.1.9. (Z)-Methyl 3-[1-(3,4-dimethoxybenzyloxy)ethyl]-4-tert-butyldimethylsilyloxymethyl-6-methoxy-2-(6-triisopropylsilylhexa-3-en-1,5-diynyl)quinoline-1(2H)-carboxylate (**17b**).* To a solution of enediyne **16** (550 mg, 2.36 mmol, 1.2 equiv) in dry THF (5 mL) at 0 °C was added a solution of ethylmagnesium bromide 1 M in THF (2.36 mL, 2.36 mmol, 1.2 equiv). The mixture was warmed to room temperature for 2 h then cooled to −18 °C. A solution of **15** (980 mg, 1.97 mmol, 1 equiv) in THF (5 mL) and methyl chloroformate (182 μL, 2.36 mmol, 1.2 equiv) were then added to the reaction mixture. After 1 h water was added and the product was extracted with Et_2O (three times). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to leave brown oil. The product was purified by column chromatography on silica gel using PE/EtOAc 4:1 as eluent to afford **17b** as a mixture of two diastereoisomers (6:4) as a yellow oil (1.34 g, **86**%). The two diastereoisomers were separated by medium pressure liquid chromatography using an 80 g column of silica gel (15 μm) loading at 0.5% and PE/EtOAc 9:1 as eluent (flow=60 mL/min).Compound **17b**-*trans*: R_f=0.19 (PE/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, 55 °C) δ 0.14 (s, 3H), 0.15 (s, 3H), 0.97 (s, 9H), 1.19 (s, 18H), 1.20 (s, 3H), 1.52 (d, J=6.5, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 3.95 (s, 3H), 4.38 (d, J=11.8, 1H), 4.58 (d, J=11.8, 1H), 4.74 (d, J=11.8, 1H), 4.77 (d, J=11.8, 1H), 4.80 (q, J=6.5, 1H), 5.61 (dd, J=11.0, 2.0, 1H), 5.77 (d, J=11.0, 1H), 6.35 (s, 1H), 6.80–6.94 (m, 2H), 6.97 (dd, J=8.2, 1.8, 1H), 7.02 (d, J=1.7, 1H), 7.19 (d, J=2.8, 1H), 7.61 (d, J=7.0, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ −5.4, −5.2, 11.4, 18.3, 18.7, 21.3, 25.9, 43.8, 53.0, 55.5, 56.0, 56.1, 58.4, 71.2, 72.8, 79.2, 95.0, 99.6, 103.7, 109.7, 111.4, 111.6, 113.4, 119.6, 119.8, 120.1, 125.7, 128.3, 129.7, 130.6, 131.8, 148.7, 149.3, 153.4, 156.6. HRMS (ESI) $[M+Na]^+$: calcd for $C_{45}H_{65}NO_7Si_2Na$ 810.4197, found 810.4191.Compound **17b**-*cis*: R_f=0.18 (PE/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, 55 °C) δ 0.15 (s, 6H), 0.97 (s, 9H), 1.20 (s, 18H), 1.20 (s, 3H), 1.60 (d, J=6.7, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.28 (d, J=11.7, 1H), 4.54 (d, J=11.7, 1H), 4.62 (s, 2H), 4.76 (q, J=6.7, 1H), 5.69 (dd, J=11.0, 2.1, 1H), 5.81 (d, J=11.0, 1H), 6.41 (s, 1H), 6.88–6.95 (m, 3H), 7.03 (s, 1H), 7.18 (d, J=2.8, 1H), 7.61 (d, J=8.5, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ −5.2, 11.4, 18.3, 18.7, 20.8, 25.9, 43.7, 53.0, 55.5, 56.1, 56.1, 58.1, 70.4, 71.3, 80.5, 94.8, 99.6, 103.8, 110.0, 111.6, 111.6, 113.6, 119.6, 119.7, 120.2, 125.4, 128.3, 129.7, 131.2, 131.4, 148.9, 149.4, 153.7, 156.6. HRMS (ESI) $[M+Na]^+$: calcd for $C_{45}H_{65}NO_7Si_2Na$ 810.4197, found 810.4192.

*4.1.10. (Z)-Methyl 1a-[1-(3,4-dimethoxybenzyloxy)ethyl]-7b-formyl-2-(hexa-3-en-1,5-diynyl)-6-methoxy-1a,2-dihydrooxireno[2,3-c]quinoline-3(7bH)-carboxylate (**20**).* To a solution of **17b**-*cis* (1.60 g, 2.03 mmol, 1 equiv) in THF (12 mL) at 0 °C was added TBAF (1 M solution in THF, 4.5 mL, 4.50 mmol, 2.2 equiv). After 1 h, water was added and the product was extracted with Et_2O (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to leave a brown oil. The crude oil was purified by column chromatography on silica gel using PE/EtOAc 2:3 as eluent to afford (*Z*)-methyl 3-[1-(3,4-dimethoxybenzyloxy)ethyl]-2-(hexa-3-en-1,5-diynyl)-4-hydroxymethyl-6-methoxyquinoline-1(2*H*)-carboxylate as a yellow oil (0.95 g, **90**%). R_f=0.46 (PE/EtOAc 2:3). ^{1}H NMR (300 MHz, $CDCl_3$, 55 °C) δ 1.54 (d, J=6.7, 3H), 1.74 (s, 1H), 3.05 (dd, J=2.0, 0.5, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.27 (d, J=11.6, 1H), 4.48 (d, J=11.6, 1H), 4.51 (d, J=12.4, 1H), 4.61 (q, J=6.7, 1H), 4.62 (d, J=12.4, 1H), 5.64 (dd, J=11.0, 2.0, 1H), 5.71 (ddd, J=11.0, 1.7, 0.5, 1H), 6.24 (d, J=1.7, 1H), 6.80–6.88 (m, 3H), 6.93 (d, J=1.6, 1H), 7.10 (d, J=2.8, 1H), 7.55 (d, J=9.0, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ 20.8, 44.4, 53.1, 53.3, 55.6, 56.1, 57.6, 70.7, 71.8, 80.4, 84.7, 94.5, 109.7, 111.6, 111.8, 113.4, 119.0, 120.4, 121.0, 125.6, 128.3, 129.1, 130.8, 131.2, 139.1, 149.0, 149.4, 153.7, 156.8. HRMS (ESI) $[M+Na]^+$: calcd for $C_{30}H_{31}NO_7Na$ 540.1993, found 540.1993. To a mixture of molecular sieves 4 Å in powder (900 mg) in dry CH_2Cl_2 (10 mL) at −20 °C were added titanium isopropoxide (535 μL, 1.80 mmol, 1.1 equiv) and TBHP (5 M solution in octane, 700 μL, 3.50 mmol, 2.5 equiv). After 30 min, a solution of (*Z*)-methyl 3-[1-(3,4-dimethoxybenzyloxy)ethyl]-2-(hexa-3-en-1,5-diynyl)-4-hydroxymethyl-6-methoxyquinoline-1(2*H*)-carboxylate (850 mg, 1.64 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred at −20 °C for 5 h before being quenched with water. The product was then extracted with Et_2O (three times) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel using PE/EtOAc 1:1 as eluent to give (*Z*)-methyl 1a-[1-(3,4-dimethoxybenzyloxy)ethyl]-2-(hexa-3-en-1,5-diynyl)-7b-(hydroxymethyl)-6-methoxy-1a,2-dihydrooxireno[2,3-*c*]quinoline-3(7b*H*)-carboxylate as a pale yellow oil (455 mg, **52**%). R_f=0.38 (PE/EtOAc 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 1.48 (d, J=6.7, 3H), 2.31 (t, J=6.2, 1H), 3.09 (d, J=0.7, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.07 (dd, J=12.7, 6.0, 1H), 4.19 (q, J=6.7, 1H), 4.26 (dd, J=12.6, 7.5, 1H), 4.55 (d, J=11.0, 1H), 4.67 (q, J=11.0, 1H), 5.69 (s, 2H), 5.97 (s, 1H), 6.81–6.87 (m, 2H), 6.91 (dd, J=8.1, 1.8, 1H), 6.94–6.96 (m, 1H), 7.25 (br s, 1H), 7.27 (d, J=2.8, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 18.2, 30.4, 46.5, 53.4, 55.6, 56.0, 56.0, 60.9, 61.0, 71.9, 74.8, 76.9, 80.3, 81.9, 85.1, 92.5, 111.5, 112.0, 113.8, 113.9, 119.7, 120.5, 120.8, 128.1, 128.3, 129.5, 130.3, 149.1, 149.4, 157.3. HRMS (ESI) $[M+Na]^+$: calcd for $C_{30}H_{31}NO_8Na$ 556.1942, found 556.1943.

To a solution of (*Z*)-methyl 1*a*-[1-(3,4-dimethoxybenzyloxy)ethyl]-2-(hexa-3-en-1,5-diynyl)-7b-(hydroxymethyl)-6-methoxy-1a,2-dihydrooxireno[2,3-*c*]quinoline-3(7b*H*)-carboxylate (250 mg, 0.47 mmol, 1 equiv) in dichloromethane (5 mL) was added Dess–Martin periodinane (400 mg, 0.94 mmol, 2 equiv) at 0 °C. The mixture was stirred at room temperature for 30 min then diluted with dichloromethane and the organic layer washed with an aqueous $Na_2S_2O_3$ solution and brine. The combined aqueous layers were extracted with EtOAc (two times) and the combined organic layers washed with brine then dried over $MgSO_4$. After filtration solvent was removed under reduced pressure and the crude oil was purified by column chromatography on silica gel using PE/EtOAc 1:1 as eluent to afford **20** as a pale yellow oil (245 mg, **99**%). R_f=0.51 (PE/EtOAC 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 1.45 (d, J=6.6, 3H), 3.19 (d, J=1.8, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.19 (q, J=6.6, 1H), 4.37 (d, J=11.7, 1H), 4.43 (d, J=11.7, 1H), 5.68 (dd, J=11.0, 1.6, 1H), 5.74 (dd, J=11.0, 2.2, 1H), 5.84 (s, 1H), 6.81 (d, J=8.0, 1H), 6.84 (dd, J=8.0, 1.9, 1H), 6.87–6.90 (m, 2H), 7.27 (s, 1H), 7.38 (d, J=2.5, 1H), 9.59 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 16.8, 46.1, 53.6, 55.6, 56.0, 63.7, 70.8, 71.4, 80.1, 81.6, 82.8, 85.6, 90.6, 111.3, 111.9, 113.2, 114.9, 120.1, 120.6, 120.8, 123.8, 128.5, 128.8, 129.8, 149.1, 149.3, 157.1, 194.0. HRMS (ESI) $[M+Na]^+$: calcd for $C_{30}H_{29}NO_8Na$ 554.1785, found 554.1786.

*4.1.11. Cyclized product (**4bb**).* To anhydrous cerium chloride (167 mg, 0.68 mmol, 4 equiv) was added a solution of **20** (90 mg, 0.17 mmol, 1 equiv) in dry THF (3.4 mL, 0.05 M) at room temperature and under argon. After 30 min of stirring, the mixture was cooled to −78 °C and a solution of KHMDS (0.5 M in toluene,

510 μL, 0.26 mmol, 1.5 equiv) was added slowly. The reaction was allowed to warm to −40 °C then poured into a separated funnel containing an aqueous saturated NH_4Cl solution. EtOAc was added and the organic layer was washed with a 5% acetic acid solution and the combined aqueous layers extracted with EtOAc (three times). The combined organic layers was washed with brine, saturated aqueous $NaHCO_3$ and brine then dried over $MgSO_4$. After filtration solvent was removed under reduced pressure and the crude oil was purified by preparative thin layer chromatography on silica gel using PE/EtOAc 1:4 as eluent to afford **4bb** as a pale yellow oil (31 mg, **34**%). R_f=0.52 (PE/EtOAc 1:4). ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 1.54 (d, J=6.9, 3H), 2.43 (d, J=3.7, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 3.98 (q, J=6.9, 1H), 4.50 (d, J=11.0, 1H), 4.74 (d, J=11.0, 1H), 5.26 (s, 1H), 5.64–5.68 (m, 1H), 5.77 (d, J=10.1, 1H), 5.97 (s, 1H), 6.82–6.86 (m, 2H), 6.93–6.96 (m, 1H), 7.06 (s, 1H), 7.27 (s, 1H), 8.05 (d, J=2.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 19.9, 46.0, 53.3, 55.5, 55.9, 64.8, 65.1, 71.9ESI) $[M+Na]^+$: 75.0, 76.8, 90.3, 92.5, 95.7, 98.8, 110.8, 110.9, 111.6, 111.7, 111.9, 113.7, 116.5, 121.0, 122.9, 123.5, 128.5, 129.8, 130.5, 148.7, 149.0, 156.3. HRMS (calcd for $C_{30}H_{29}NO_8Na$ 554.1785, found 554.1785.

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Supplementary data

Full details of the experimental procedures including ^{1}H, ^{13}C NMR spectra and HRMS data. CCDC reference number 771190 for **12** and 746985 for **14**-*cis*, contain the supplementary crystallographic data for this paper. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.090.

References and notes

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