Intramolecular Imino Diels-Alder Reaction: Progress toward the Synthesis of Uncialamycin

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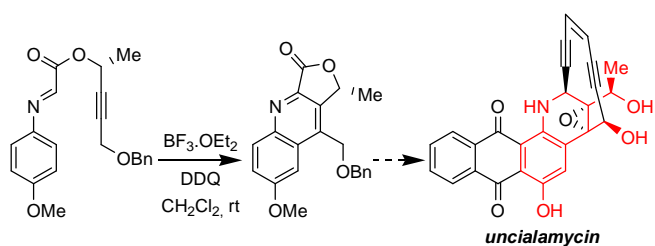
ABSTRACT. We herein described an intramolecular imino Diels-Alder reaction promoted with $BF_3.OEt_2$/DDQ affording substituted quinolines. Using this procedure, we prepared the chiral quinoline moiety of the uncialamycin, a new enediyne natural product.

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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 a lichen *Cladonia uncialis*.[1] First biological evaluations shown that **1** possess potent in vitro antibacterial activity against *Staphylococcus aurens*, *Escheridia coli* and *Burkholderia apia*. Despite of the small amount of product available (~300 μg were isolated) 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.

The structure of uncialamycin **1,** similar to the dynemicin A **2**,[3] combines a ten-membered enediyne with an anthraquinone substructure. The strategy for the total synthesis of the title compound **1** described by Nicolaou and co-workers was based on the addition of an acetylide to a quinolinium species, an intramolecular acetylide addition affording the enediyne system and then an Hauser annulation to complete the synthesis. The first key synthetic intermediate, the chiral quinoline moiety, was prepared from the commercially available 5-methoxyisatin including a Friedländer quinoline synthesis and an enantioselective reduction of ketone to fix the stereogenic center C26.[2]
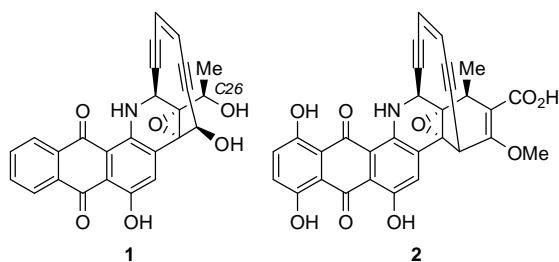

FIGURE 1. Structures of uncialamycin (**1**) and dynemicin A (**2**).

These recent findings prompt us to report our progress toward the synthesis of the title compound **1**. Our approach focused on the preparation of a quinoline which possess the well-defined chiral center C26. The quinoline and tetrahydroquinoline derivatives still attracted interest due to their importance as synthetic intermediates and as key structural core in several natural products which have shown a wide range of biological activities.[4] Hence a variety of synthetic routes have been reported and the development of new approaches still remains an active field of research. Classical methods, such as Friedländer, Combes, Skraup and Doeber-Miller reactions are widely recognized and frequently used for the preparation of quinolines from anilines but they do not allow the formation of the quinoline nucleus with diversity. In addition, the harsh reaction conditions can lead to several by-products and sometimes poor yields.[5,6] The recent development of alternative methods have been reported by the use of transition metal as catalysts and some drawbacks have been overcome.[7] Among these methods, one the most direct to built quinoline scaffolds consist to add electron-rich alkenes (or alkynes) to electron-defficient aromatic imines (formed in situ from aniline and aldehyde derivatives) followed by an oxidation reaction (Scheme 1). Although this imino Diels-Alder reaction, also called Povarov reaction, was first reported about 40 years ago, this reaction only recently received more attention since it was shown that this cycloaddition reaction can be promoted or catalyzed by Lewis or protic acids. However its use in total synthesis still remains scarce.[8]

SCHEME 1. **Quinolines preparation from Povarov reaction.**
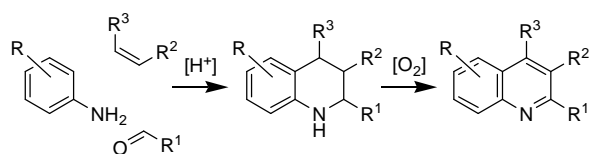
For example, the total synthesis of the alkaloid martinelline was simultaneously reported by Batey[9a] and Ma.[9b] Mixing the methyl 4-aminobenzoate with 2 equiv of *N*-Cbz 2-pyrroline in the presence of 5 mol % of camphor sulfonic acid, Batey and co-workers isolated the tetrahydroquinoline core of martinelline whereas Ma and co-workers combined the methyl 4-aminobenzoate with ethyl glyoxalate and *N*-Cbz 2,3-dihydro-1*H*-pyrrole in the presence of squaric acid, an unusual catalyst to lead to the

tetrahydroquinoline nucleus. The intramolecular Povarov reaction catalyzed by Dy(OTf)$_3$ has also been used to prepare the alkaloids luotonin A which possess a quinoline core.[10] The intramolecular Povarov reaction was also developed in combinatorial synthesis providing chemical librairies built around the quinoline scaffold.[11]

Having these different approaches in mind, we report a detailled account of the use of intramolecular imino Diels-Alder reactions to prepare polysubstituted quinolines. Relying on these results we describe our work for the construction of the quinoline core of the uncialamycin **1**.

Results and Discussion

Intramolecular imino Diels-Alder reaction. In order to built the quinoline intermediate via the most simple and quickest pathway, we first investigated the reactivity of 1,3,5-tri(*p*-methoxyphenyl)-hexahydro-1,3,5-triazene **3**[12] with the alkene **4**[13] or alkyne **5**[13] in the presence of Lewis acid (Scheme 2). Although a few examples of [4+2] cycloaddition has been described between aromatic methyleneamines in its trimer form and dienophiles,[14] no cycloadduct was formed after stirring in various reaction conditions with the alkene **4** or alkyne **5**. This lack of reaction could be either due to the low reactivity of the triazine **3** or to the electronic character of the dienophile which is not electron-rich enough.
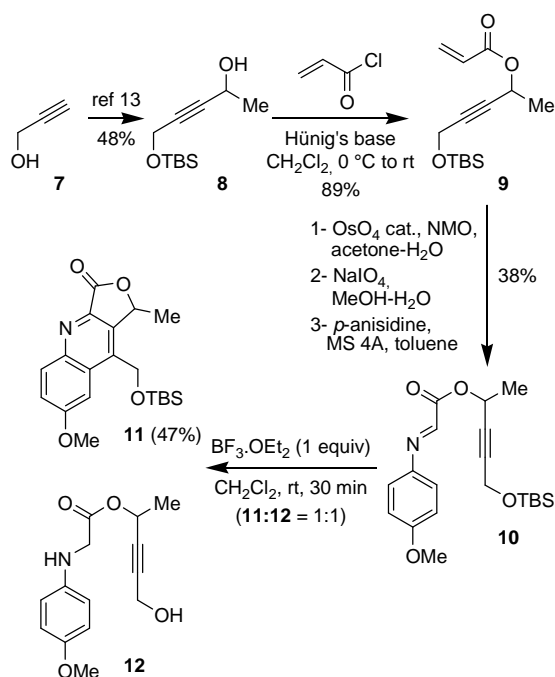
SCHEME 2. **Unsuccessfull imino Diels-Alder reaction.**

Ar = *p*-MeO-C$_6$H$_4$
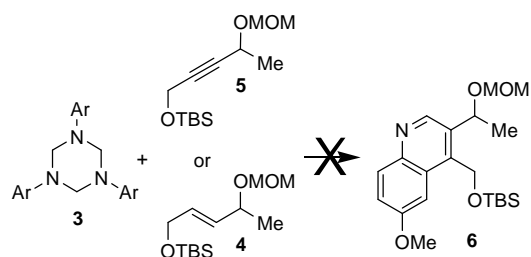
Because the dienophile **4** or **5** is not electron-rich enough to react with an aromatic methyleneamine we thought to study the intermolecular cycloaddition with a more electron deficient *N*-aryl imine, such as *p*-anisidine ethylglyoxylate imine derivatives.[15] Again, although different reaction conditions have been tested (Lewis acid, solvent and temperature) the formation of cycloadduct was not observed. Face this failure, we planned to realize the same reaction in its intramolecular version. We felt that there were

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two major advantages to evaluate this intramolecular cycloaddition. As in intramolecular cycloaddition, the diene and the dienophile will be close to each other, this reaction should be allowed and only one regioisomer would be obtained. As shown in Scheme 3, the precursor of cycloaddition **10** was synthesized in few step from the propargyl alcohol **7**. Reaction of the acryloyl chloride in the presence of Hünig's base with the racemic alcohol **8** gave the acryloyl ester **9**. After osmylation of **9** the intermediate diol was obtained in 78% yield and then quantitatively converted into the corresponding glyoxal by using an excess of sodium periodate. The imine **10** was isolated in 50% yield after addition of *p*-anisidine to the crude glyoxal in toluene in the presence of molecular sieves.[16] When the coumpound **10** was treated with one equivalent of $BF_3.OEt_2$ in CH_2Cl_2 at room temperature, the formation of a mixture of the expected quinoline **11** with the amine **12** in ratio 1:1 (determined from the crude reaction mixture by ^{1}H NMR) was observed after complete disappearance of the starting material. The derivative **11** was isolated in 47% yield while the desilylated amine **12** decomposed during the purification. This result demonstrates that the intramolecular imino Diels-Alder favorizes the cycloaddition. The presence of the amine **12** suggests that half equivalent of imine **10** reacts as an oxidant to convert the intermediate dihydroquinoline in quinoline **11**. During our work, similar observations were reported by Takasu and co-workers in course of their studies of a catalytic Povarov reaction.[17] They proposed that Tf_2NH catalyzes two distinct reactions: a cycloaddition between aldimines and electron-rich olefins to give the corresponding tetrahydroquinolines in-situ and in the same time an hydrogen-transfer process from tetrahydroquinolines to aldimines affording the resulting quinolines and amines.

SCHEME 3. **First attempted intramolecular cycloaddition reaction.**

ref 13
48%

Hünig's base
CH₂Cl₂, 0 °C to rt
89%

$$\text{OH} \quad \text{Me} \quad \text{OTBS} \quad \textbf{8}$$

7

9

1- OsO₄ cat., NMO, acetone-H₂O
2- NaIO₄, MeOH-H₂O
3- *p*-anisidine, MS 4A, toluene
38%

11 (47%)

BF₃.OEt₂ (1 equiv)
CH₂Cl₂, rt, 30 min
(**11:12** = 1:1)

10

12

The imines **13** and **14** were prepared as previously reported from tartaric acid[13,18] and subjected to the same reaction conditions as above. The imine **13** led to the quinoline **15** and the amine **16** in a **15/16** = 0.33:0.66 ratio while **14** gave **15** and **17** in a **15/17** = 0.5:0.5 ratio and the tetrahydroquinoline **18** and the dihydroquinoline **19** were not detected in the crude reaction mixture (Scheme 4). This means that the oxidation of cycloadduct by the imine proceeds in the same rate as the intramolecular cycloaddition. These results confirm the double role played by the starting material: the imine acts as precursor of the cycloadduct as well as an oxidant to convert the resulting cycloadduct into quinoline. Therefore the presence of an oxidant which could react faster than the imine in the reaction mixture has been envisaged. Thus, we examined the intramolecular cycloaddition reaction of imine **13** with BF₃.OEt₂ (1 equiv) in CH₂Cl₂ in the presence of various oxidants. As shown in Scheme 5, the reaction works well in the presence of 2 equiv of DDQ to afford the quinoline **15** in good yield (72%) without any traces of amine **16**. In the presence of one equiv of DDQ a complex reaction mixture was obtained. This confirms the need of using two equivalents of oxidant for cycloaddition from alkenes. When the DDQ was replaced with O₂ (1 atm or bubbling O₂ in the reaction mixture), a complex mixture was obtained and the quinoline was isolated in very low yield (up to 23%). Hoping that CAN could be act both as promoter of the imino Diels-Alder reaction[19] and oxidant, the imine **13** was placed in the presence of 2.1

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equiv CAN in CH$_2$Cl$_2$. Although the disappearance of **13** was complete, only a low amount of quinoline **15** was isolated after purification on silica gel column chromatography from a complex reaction mixture (26% yield). Having found a satisfactory system, we turned our attention to the amount of BF$_3$.OEt$_2$ required to achieve this intramolecular imino Diels-Alder reaction in good yields. When the imine **13** with 2 equiv DDQ in the presence of 1, 0.5, 0.2 or 0.1 equiv BF$_3$.OEt$_2$ was carried out in CH$_2$Cl$_2$ at room temperature after stirring 1 h, the chemical yield slighty decreased (72%, 63%, 54% and 58% respectively). In the absence of BF$_3$.OEt$_2$, no quinoline was formed and only decomposition of the starting material was observed.

SCHEME 4. **Cycloaddition reactions.**
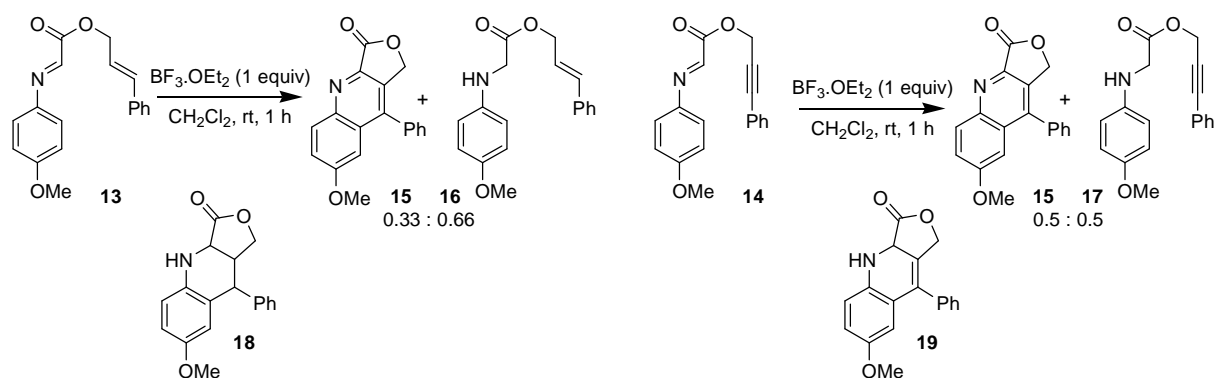

SCHEME 5. **Choice of the oxidant.**
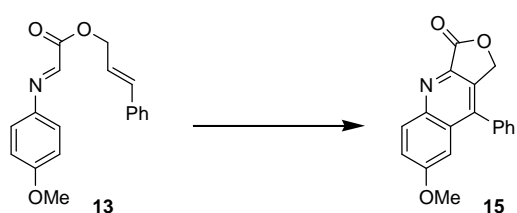
conditions	
BF$_3$.OEt$_2$ (1 equiv), DDQ (2 equiv), CH$_2$Cl$_2$, rt, 1 h	72%
BF$_3$.OEt$_2$ (1 equiv), O$_2$, CH$_2$Cl$_2$, rt, 1 h	23%
CAN (2.1 equiv), CH$_2$Cl$_2$, rt, 1 h	26%

Whereas the BF$_3$.OEt$_2$ (1 equiv)/DDQ (2 equiv for alkenes and 1 equiv for alkynes) appears as the best compromise to built quinolines using an intramolecular Povarov reaction, we then examined the reactivity of other substrates in these reaction conditions. For this purpose we prepared some precursors by varying the aromatic groups and the dienophile that is either an olefin or an alkyne. The glyoxilic acid

moiety was synthesized following two different routes, from the tartaric acid **20** for the alkenes'

derivatives **23** and from the acryloyl chloride for alkynes' compounds **28** (Scheme 6). As the glyoxylic

and imine's intermediates are not easy to isolate pure, we chose to determine the yields of the synthesis

of quinoline **30** from **22** and **27**. The ^{1}H NMR spectral data were consistent with expectations for the

proposed structures **25** and **29** and revealed that the products have been formed in good to quantitative

conversion.

SCHEME 6. **General scheme of quinoline synthesis**.
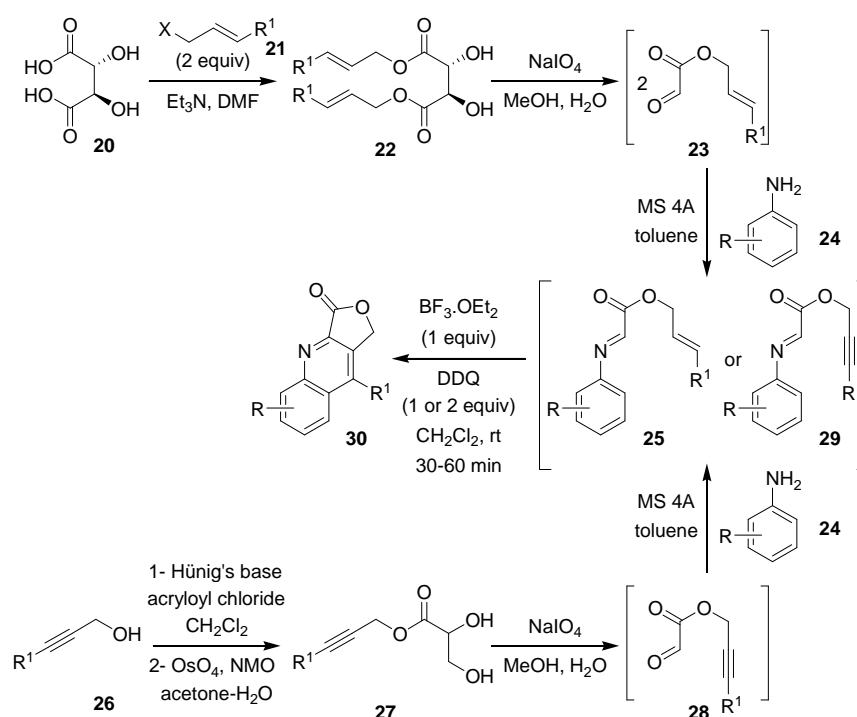
We first investigated the influence of the electron density of the aromatic group on the cycloaddition

reaction. Various imine derivatives were synthesized from the cinnamyl glyoxylate **23a** as outlined in

Scheme 6. The results of this study are reported in Table 1. As indicated above, the yield of the

formation of quinolines were determined from the dicinnamyl tartrate **22** obtained after purification in

72% yield. The intramolecular imino Diels-Alder reaction of the crude mixture of **25** was carried out in

presence of 1 equiv BF$_3$.OEt$_2$ and 2 equiv DDQ in CH$_2$Cl$_2$ at room temperature. The preparation of

imine derivatives **25** works well in most cases (complete conversion) except when using the 4-nitro

aniline for in which case no reaction was observed. The quinolines **30** were isolated in low to good

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yields however it appears difficult to rationalize the results based to the electronic density of the aryl group. The electron-rich imine **13** gave the best result (72% yield over 3 steps) and in the same time the electron-defficient imine **25ag** (R = F) afforded 65% yield in quinoline **30ag**.

TABLE 1. Scope of the aromatic group
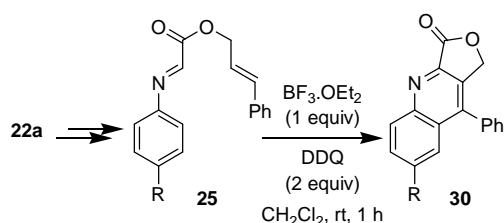
entry	R	yield, %	product
1	OMe	72	**15**
2	H	24	**30ab**
3	Me	47	**30ac**
4	NMe$_2$	N.R.[a]	**30ad**
5	Cl	57	**30ae**
6	CF$_3$	55	**30af**
7	F	65	**30ag**
8	NO$_2$	N.R.[b]	**30ah**

[a] no cycloaddition. [b] no imine formation.

We then compared the intramolecular cycloaddition between alkenes **25** and alkynes **29**. Various compounds were prepared as decribed in Scheme 6. As shown in Table 2 the reaction sequence afforded low to good yields. Except with the terminal olefine and alkyne (entries 1 and 2), we observed a good conversion of the crude imine **25** or **29** into quinoline **30**. The moderate yields are due to an incomplete conversion of the diol **22** or **27** into glyoxilic derivative **23** or **28**. It is noteworthy that there is no significant difference between the alkenes' route and the alkynes'route. Because only one equiv of DDQ is required, it seems more interesting to use the latest.

TABLE 2. Alkene vs alkyne
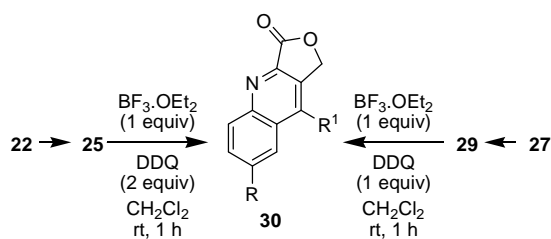
entry	R	R^1	yield, % from 22	yield, % from 27	product
1	H	H	N.R.[a]	N.R.[a]	**30ba**
2	OMe	H	15	< 5[b]	**30bb**
3	OMe	n-Pr	32	44	**30bc**
4	H	Ph	24	56	**30ab**
5	OMe	Ph	72	59	**15**
6	OMe	CH$_2$OBn	-	64	**30bd**

[a] 48-50% conversion of the imine formation and no cycloaddition. [b] determined by ^{1}H NMR.

Preparation of the quinoline core of uncialamycin. Relying on these various results, we decided to prepare the quinoline core of uncialamycin **1** from the alkyne ketone **31**.[20] Enantioselective reduction of **31** with (R)-Alpine borane according to Brown[21] afforded cleanly the alcohol **32** with 80% e.e. as determined from the ^{1}H NMR after derivatisation into its corresponding O-methylmandelic ester **38**.[22] The alkynol **32** was quantitatively converted in acryloyl ester **33** and the diol **34** was isolated as a diastereomeric mixture after osmylation reaction in 55% yield. The diol **34** was converted into its glyoxilic acid derivative which was treated with p-anisidine in toluene in the presence of molecular sieves to give the imine **35**. After imino Diels-Ader cycloaddition the quinoline **36** was isolated in 65% yield overall from the diol **34** with 89% e.e. as determined by HPLC.[23]

SCHEME 7. **Prepation of the chiral quinoline 36**

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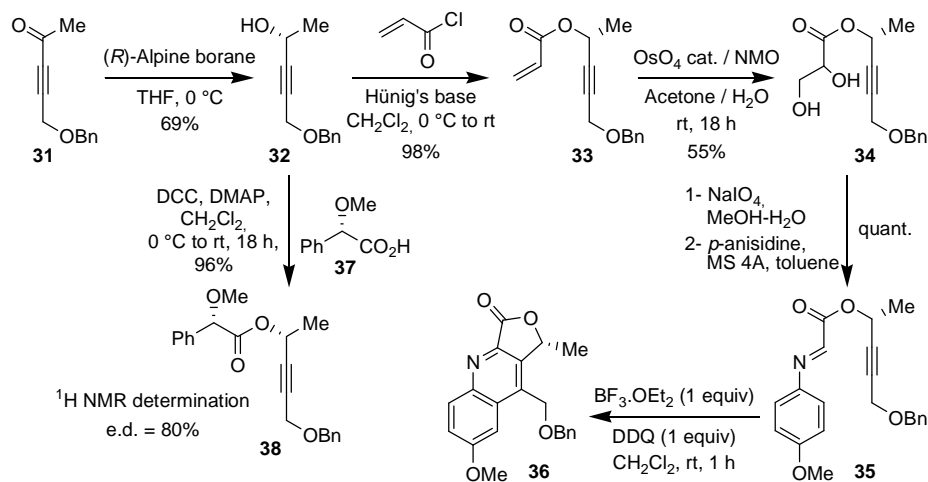
Finally, to confirm the formation of the quinoline, the lactone opening of the racemic quinoline **39**[13] was carried out with an excess of methyl magnesium chloride to afford the gem-dimethyl alcohol **40**. Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of dichloromethane at room temperature from an ethanol/dichloromethane solution of **40**. The X-ray crystal structure analysis of **40** shows the expected quinoline core (Scheme 8).

SCHEME 8. Synthesis of quinoline 40 and ORTEP drawing of 40.
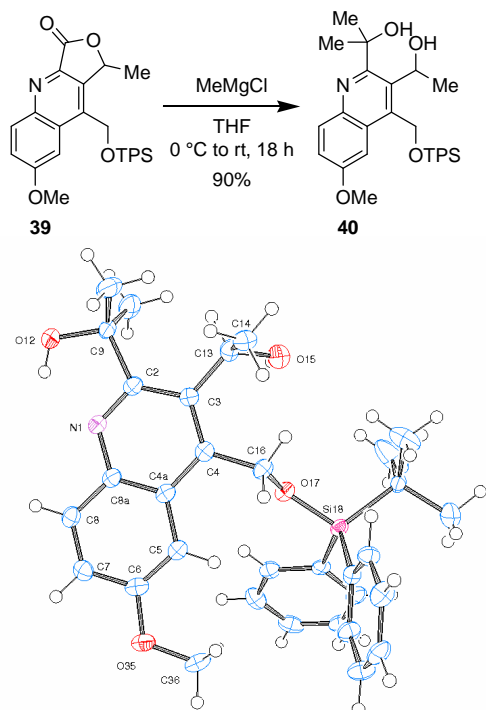
Conclusions

In summary, we have described that $BF_3.OEt_2$ in the presence of DDQ promotes intramolecular Povarov reaction and oxidative aromatization affording substituted quinolines. The dienophile could be either an alkene or an alkyne without the yield of cyclisation was affected. One equiv of DDQ is necessary in the case of the cycloaddition reaction with the alkynes while it takes two equiv for the reaction with alkenes. In the absence of DDQ, the cycloaddition reaction occurs but the quinoline was obtained in mixture with an amine which results of a hydrogen transfer from the dihydro- or tetrahydroquinoline to the starting imine.

These reaction conditions were used to prepare the chiral quinoline moiety of the enediyne uncialamycin **1**. The C26 chiral center of the uncialamycin was fixed at the beginning of the synthesis from a well known enantioselective reduction of α-alkyne ketone.

Overall, we believe that the described intramolecular imino Diels-Alder reaction will allow a rapid access to polysubstituted quinolines in a simple and straightforward way.

Experimental Section

All reagents of high quality were purchased from commercial suppliers, and used without further purification. DMF and toluene were distilled from CaH_2 and THF from Na/benzophenone. ^{1}H and ^{13}C NMR were recorded at 270 and 67.5 MHz respectively, using $CDCl_3$ (and TMS 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; d, doublet; t, triplet; q, quadruplet; sext, sextet ; dd, doublet of doublet ; dt, doublet of triplets ; dq, doublet of quartets ; m, multiplet ; bs, broad singlet. Thin layer chromatography was performed using precoated silica gel plate (0.2 mm thickness). Chiral HPLC was performed using a Chiralpak AD-H column (5 µ, 4.6 x 250 mm) with a UV detection at 298 nm. Melting points were obtained on a hot bench.

General procedure for intramolecular imino Diels-Alder reaction: preparation of quinoline 15 from 13 (Table 1, entry 1). To a 0.2 M solution of the crude imine **13** in dichloromethane under argon atmosphere at R.T. was added 2 eq. of DDQ and then 1 eq. of $BF_3.OEt_2$. The mixture was stirred for 30 min. and the solvent was removed under reduced pressure. The dark residue was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 7:3 as eluent and by a followed recrystallization in ethanol.

Synthesis of quinoline 36 (Scheme 7).

5-(Benzyloxy)pent-3-yn-2-one (31):[24] To a solution of 1-[(prop-2-ynyloxy)methyl]benzene (3.00 g, 20.5 mmol, 1 eq.) in THF under argon atmosphere at -78 °C was added *n*-BuLi (2.5 M in hexanes, 9.03 mL, 22.6 mmol, 1.1 eq.). After 30 min. at -78 °C *N*-acetylmorpholine (4.78 mL, 41.0 mmol, 2 eq.) was added and the reaction mixture was allowed to warm to R.T. overnight. The reaction was then quenched with a saturated aqueous solution of NH_4Cl. The product was extracted with ethyl acetate (3 times) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate 95:5 as eluent to obtain **31** as a colorless oil (1.35 g, 7.18 mmol, **35%**). R_f: 0.3 (cyclohexane/ethyl acetate 8:2) ; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5H), 4.61 (s, 2H), 4.32 (s, 2H), 2.36 (s, 3H) ; ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 183.9, 136.7, 128.5, 128.1, 128.0, 87.3, 85.7, 72.1, 56.9, 32.6 ; HRMS (ESI) calcd for $C_{12}H_{12}O_2Na$ 211.0735, found 211.0735.

(R)-5-(Benzyloxy)pent-3-yn-2-ol (32):[25] To a commercial solution of (*R*)-Alpine Borane® (0.5 M in THF, 8.50 mL, 4.25 mmol, 2 eq.) under argon atmosphere at 0 °C was added **31** (400 mg, 2.12 mmol, 1 eq.). The THF was removed under reduced pressure at 0 °C and the resulting oil was stirred at R.T. overnight. The mixture was cooled to 0 °C and 4 mL of diethyl ether, 0.5 mg of acetaldehyde and 0.5 mL of diethanolamine were successively added. The resulting precipitate was eliminated by filtration and the filtrate was washed with a 0.1 M aqueous solution of HCl, washed with brine, dried over

Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate 8:2 as eluent to obtain **32** as a colorless oil (280 mg, 1.47 mmol, **69%**). R$_f$: 0.2 (cyclohexane/ethyl acetate 7:3); ee = 80% ; [α]$_D^{22}$ = + 14.0 (*c* 1.0, CHCl$_3$) ; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.47-7.23 (m, 5H), 4.63-4.53 (m, 3H), 4.19 (d, *J* = 1.4 Hz, 2H), 2.21-2.05 (bs, 1H), 1.46 (d, *J* = 6.5 Hz, 3H) ; ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 137.4, 128.4, 128.1, 127.9, 88.5, 79.9, 71.7, 58.3, 57.4, 24.2 ; HRMS (EI) calcd for C$_{12}$H$_{14}$O$_2$ 190.0994, found 190.1012.

(*R*)-5-(Benzyloxy)pent-3-yn-2-yl acrylate (33): To a solution of **32** (1.00 g, 5.26 mmol, 1 eq.) and Hünig's base (2.72 mL, 15.8 mmol, 3 eq.) in 20 mL of dichloromethane at 0 °C under argon atmosphere was added acryloyl chloride (854 µL, 10.5 mmol, 2 eq.). The mixture was allowed to warm to R.T. overnight and quenched with a saturated aqueous solution of NH$_4$Cl. The product was extracted with ethyl acetate (3 times) and the combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate 95:5 as eluent to obtain **33** as a colorless oil (1.26 g, 5.16 mmol, **98%**). R$_f$: 0.4 (cyclohexane/ethyl acetate 8:2) ; [α]$_D^{22}$ = + 74.0 (*c* 1.0, CHCl$_3$) ; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.47-7.26 (m, 5H), 6.45 (dd, *J* = 16.6 and 1.4 Hz, 1H), 6.13 (dd, *J* = 16.6 and 10.5 Hz, 1H), 5.86 (dd, *J* = 10.5 and 1.4 Hz, 1H), 5.58 (dq, *J* = 6.8 and 1.6 Hz, 1H), 4.58 (s, 2H), 4.19 (d, *J* = 1.6 Hz, 2H), 1.54 (d, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 164.9, 137.3, 131.3, 128.4, 128.1, 128.0, 127.8, 84.8, 80.8, 71.6, 60.4, 57.2, 21.3 ; HRMS (EI) calcd for C$_{12}$H$_{14}$O$_2$ 190.0994, found 190.0993.

(*R*)-5-(Benzyloxy)pent-3-yn-2-yl 2,3-dihydroxypropanoate (34): To a mixture of **33** (1.00 g, 4.09 mmol, 1 eq.) and NMO (663 mg, 4.91 mmol, 1.2 eq.) in 30 mL of acetone/water 9:1 was added a solution of osmium tetroxide (0.5 % w/v in *tert*-butanol, 2.08 mL, 0.041 mmol, 0.01 eq.). The mixture was stirred overnight at R.T. in the dark and was quenched with a saturated aqueous solution of Na$_2$S$_2$O$_5$. The resulting mixture was extracted with ethyl acetate (3 times). The combined organic layers

were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel using cyclohexane/ethyl acetate 1:1 as eluent to obtain **34**, a mixture of 2 diastereoisomers as a pale yellow oil (630 mg, 2.26 mmol, **55%**). R_f : 0.1 (cyclohexane/ethyl acetate 1:1) ; $[\alpha]_D^{22}$ = + 59.9 (*c* 1.0, CHCl$_3$) ; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.49-7.16 (m, 5H), 5.66-5.54 (m, 1H), 4.58 (s, 2H), 4.30-4.16 (m, 3H), 3.97-3.79 (m, 2H), 3.36-3.22 (bs, 1H), 2.56-1.82 (bs, 1H), 1.56 and 1.47 (d, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 172.0, 137.2, 128.7, 128.5, 128.3 and 128.2 (2 dias), 128.1 and 128.0 (2 dias), 84.0, 81.8 and 81.7 (2 dias), 71.7and 71.6 (2 dias), 64.0, 62.3, 57.2, 21.3 ; HRMS (EI) calcd for $C_{12}H_{12}O$ 172.0888, found 172.0900.

(*R*)-5-(Benzyloxy)pent-3-yn-2-yl 2-(4-methoxyphenylimino)acetate (35): To a solution of **34** (540 mg, 1.94 mmol, 1 eq.) in 10 mL of THF/water 9:1 at R.T. was added sodium periodate (830 mg, 3.88 mmol, 2 eq.). The mixture was stirred overnight at R.T. and the iodine salts were removed by filtration through a pad of celite. A saturated aqueous solution of $Na_2S_2O_5$ was added to the filtrate and the resulting mixture was extracted with diethyl ether (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. To a solution of this yellow oil in 8 mL of toluene under argon atmosphere at R.T. was added 5 g of molecular sieves 4 Å in powder and *p*-anisidine (240 mg, 1.94 mmol, 1 eq.). The resulting mixture was stirred overnight at R.T. and the molecular sieves was removed by filtration. The filtrate was concentrated under reduced pressure to obtain **35** as a yellow oil (680 mg, quant.) which was not purified and isolated. R_f : 0.5 (cyclohexane/ethyl acetate 1:1) ; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.96 (s, 1H), 7.45-7.22 (m, 7H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.75 (q, *J* = 6.8 Hz, 1H), 4.60 (s, 2H), 4.21 (s, 2H), 3.84 (s, 3H), 1.65 (d, *J* = 6.8 Hz, 3H).

(*R*)-9-(Benzyloxymethyl)-7-methoxy-1-methylfuro[3,4-*b*]quinolin-3(1*H*)-one (36): To a solution of crude imine **35** (682 mg, 1.94 mmol, 1 eq.) in 12 mL dichloromethane under argon atmosphere at R.T. was added DDQ (440 mg, 1.94 mmol, 1 eq.) and BF$_3$.OEt$_2$ (244 µL, 1.94 mmol, 1 eq.). The mixture was

stirred for 30 min. and the solvent was removed under reduced pressure. The dark residue was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 7:3 as eluent and by a followed recrystallyzation in ethanol to obtain **36** as a light yellow solid (440 mg, 1.26 mmol, **65%** over 3 steps). R_f: 0.3 (cyclohexane/ethyl acetate 1:1) ; mp 174-176 °C ; ee = 89% ; $[\alpha]_D^{22}$ = -12.8 (*c* 1.0, CHCl$_3$) ; ^{1}H NMR (270 MHz, CDCl$_3$) δ 8.28 (d, *J* = 9.5 Hz, 1H), 7.48 (dd, *J* = 9.5 and 2.4 Hz, 1H), 7.43-7.34 (m, 5H), 7.19 (d, *J* = 2.4 Hz, 1H), 5.90 (q, *J* = 6.5 Hz, 1H), 5.06 (ABq, *J* = 13.0 Hz, 2H), 4.72 (ABq, *J* = 11.6 Hz, 2H), 3.93 (s, 3H), 1.69 (d, *J* = 6.5 Hz, 3H) ; ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 168.2, 160.0, 146.1, 142.1, 137.7, 136.7, 136.4, 133.0, 128.9, 128.6, 128.3, 128.1, 123.6, 101.1, 76.8, 73.6, 65.8, 55.6, 21.1 ; HRMS (EI) calcd for C$_{21}$H$_{19}$NO$_4$ 349.1314, found 349.1313.

Supporting Information Available: Full details experimental procedures including ^{1}H, ^{13}C spectra and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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