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

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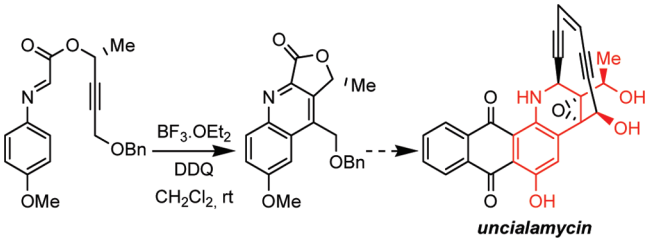

We herein described an intramolecular imino Diels−Alder reaction promoted with $BF_3 \cdot OEt_2$/DDQ affording substituted quinolines. Using this procedure, we prepared the chiral quinoline moiety of the uncialamycin, a new enediyne natural product.

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] The first biological evaluations showed that **1** possesses potent in vitro antibacterial activity against *Staphylococcus aurens*, *Escheridia coli*, and *Burkholderia apia*. Despite 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 mixture 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 that of dynemicin A **2**,[3] combines a ten-membered enediyne with an anthraquinone substructure (Figure 1). 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 **4** 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 **5**, was prepared from the commercially available 5-methoxyisatin **6** including a Friedländer quinoline synthesis and an enantioselective reduction of ketone to fix the stereogenic center C26.[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 that possesses the well-defined chiral center C26. The quinoline and tetrahydroquinoline derivatives still attracted interest due to their importance as synthetic intermediates and as a 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,

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(3) Maier, M. E.; Boβe, F.; Niestroj, A. J. *Eur. J. Org. Chem.* **1999**, 1–13.

(4) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070. (b) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141–161. (c) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116–1183.

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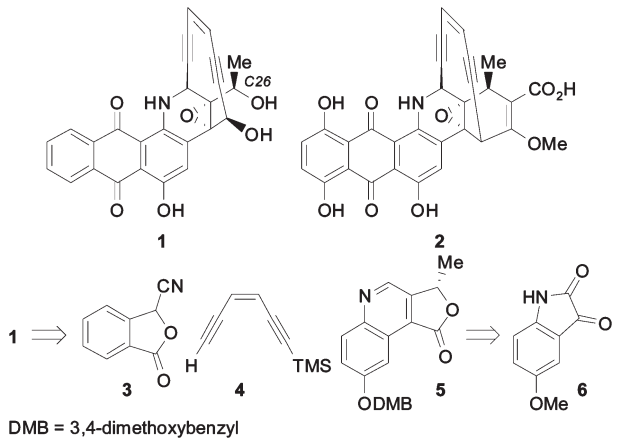
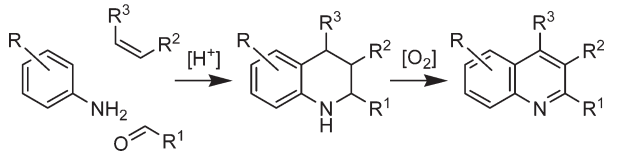


FIGURE 1. Structures of uncialamycin (**1**) and dynemicin A (**2**) and Nicolaou's retrosynthetic analysis of **1**.

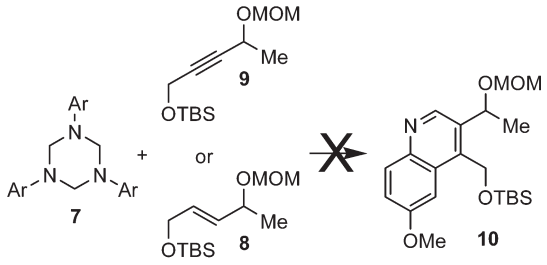
SCHEME 1. Preparation of Quinolines from the Povarov Reaction



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 byproducts and sometimes poor yields.[5,6] The recent development of alternative methods has been reported with the use of transition metal as catalysts and some drawbacks have been overcome.[7] Among these methods, the most direct to build quinoline scaffolds consists of adding electron-rich alkenes (or alkynes) to electron-deficient 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 the 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]

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]

SCHEME 2. Unsuccessful Imino Diels−Alder Reaction



Having these different approaches in mind, we report a detailed 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. To build 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 **7**[12] with the alkene **8**[13] or alkyne **9**[13] in the presence of Lewis acid (Scheme 2). Although a few examples of [4+2] cycloaddition have 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 **8** or alkyne **9**. The dienophile **8** or **9** was recovered after treatment of the reaction mixture. This lack of reaction could be due to either the low reactivity of the triazine **7** or the electronic character of the dienophile, which is not electron-rich enough.

Because the dienophile **8** or **9** 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 ethyl glyoxylate imine derivatives.[15] Again, although different reaction conditions

(5) (a) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652–2671. (b) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1996; Vol. 5, pp 167−300.

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(7) For selected recent examples, see: (a) Horn, J.; Marsden, S.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117-4120 and references cited therein. (b) Vander Mierde, H.; van der Voort, P.; De Vos, D.; Verpoort, F. *Eur. J. Org. Chem.* **2008**, 1625–1631. (c) Lekhok, K. C.; Prajapati, D.; Boruah, R. C. *Synlett* **2008**, 655–658.

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(10) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913–4916.

(11) For examples, see: (a) Spaller, M. R.; Thielemann, W. T.; Brennan, P. E.; Bartlett, P. A. *J. Comb. Chem.* **2002**, *4*, 516–522. (b) Muhuhi, J.; Spaller, M. R. *J. Org. Chem.* **2006**, *71*, 5515–5526.

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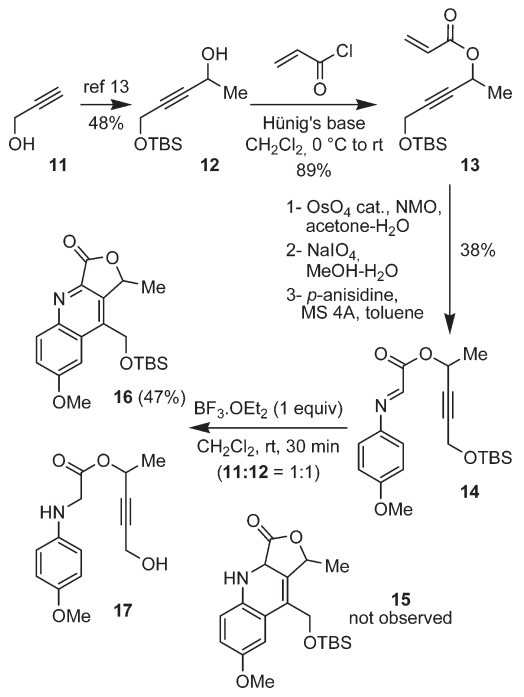
(13) See the Supporting Information.

(14) (a) Campos, P. J.; Lamaza, I.; Rodriguez, M. A. *Tetrahedron Lett.* **1997**, *38*, 6741–6744. (b) Malassene, R.; Sanchez-Bajo, L.; Toupet, L.; Hurvois, J.-P.; Moinet, C. *Synlett* **2002**, 1500–1504.

(15) For examples of [4+2] cycloaddition affording quinoline derivatives, see: (a) Alvès, M. J.; Azoia, N. G.; Fortes, A. G. *Tetrahedron* **2007**, *63*, 727–734. (b) Boglio, C.; Lemi, G.; Hasenknopf, B.; Thorimbert, S.; Lacôte, E.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3324–3327. (c) Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A. *Org. Biomol. Chem.* **2004**, *2*, 2451–2460.

SCHEME 3. First Attempted Intramolecular Cycloaddition Reaction



have been tested (Lewis acid, solvent, and temperature), the formation of cycloadduct was not observed. Facing this failure, we planned to see the same reaction in its intramolecular version. We felt that there were 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 **14** was synthesized in a few steps from the propargyl alcohol **11**. Reaction of the acryloyl chloride in the presence of Hünig's base with the racemic alcohol **12** gave the acryloyl ester **13**. After osmylation of **13** 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 **14** was isolated in 50% yield after addition of *p*-anisidine to the crude glyoxal in toluene in the presence of molecular sieves.[16] When compound **14** was treated with 1 equiv of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at room temperature, the formation of a mixture of the quinoline **16** with the amine **17** in a 1:1 ratio (determined from the crude reaction mixture by ^{1}H NMR) was observed after complete disappearance of the starting material in place of the expected dihydroquinoline **15**. The derivative **16** was isolated in 47% yield while the desilylated amine **17** decomposed during the purification. This result demonstrates that the intramolecular imino Diels−Alder favors the cycloaddition. The presence of the amine **17** suggests that half an equivalent of imine **14** reacts as an oxidant to convert the intermediate dihydroquinoline **15** in quinoline **16**. During our work, similar observations were reported by Takasu and co-workers in the 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 at the same time a hydrogen-transfer process from tetrahydroquinolines to aldimines affording the resulting quinolines and amines.

The imines **18** and **19** were prepared as previously reported from tartaric acid[13,18] and subjected to the same reaction conditions as above. The imine **18** led to the quinoline **20** and the amine **21** in a **20**/**21** = 0.33:0.66 ratio while **19** gave **20** and **22** in a **20**/**22** = 0.5:0.5 ratio and the tetrahydroquinoline **23** and the dihydroquinoline **24** were not detected in the crude reaction mixture after ^{1}H NMR analysis (Scheme 4). This means that the oxidation of cycloadduct by the imine proceeds faster or at 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 that could react faster than the imine in the reaction mixture has been envisaged. Thus, we examined the intramolecular cycloaddition reaction of imine **18** with $BF_3 \cdot OEt_2$ (1 equiv) in CH_2Cl_2 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 **20** in good yield (72%) without any traces of amine **21**. In the presence of 1 equiv of DDQ a complex reaction mixture was obtained. This confirms the need of using 2 equiv of oxidant for cycloaddition from alkenes. When the DDQ was replaced with O_2 (1 atm or bubbling O_2 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 act both as a promoter of the imino Diels−Alder reaction[19] and an oxidant, the imine **18** was placed in the presence of 2.1 equiv of CAN in CH_2Cl_2. Although the disappearance of **18** was complete, only a small amount of quinoline **20** was isolated after purification on silica gel column chromatography from a complex reaction mixture (26% yield). Having shown the importance of the presence of DDQ in the reaction mixture to obtain only the quinoline **20**, the first reaction depicted in Scheme 4 was conducted again as follows: After conversion of the imine **18** in quinoline **20** and amine **21**, 2 equiv of DDQ was added to the reaction mixture. After an additional 1 h of stirring, the amine **21** was totally converted to quinoline **20**. This experiment seems to indicate here that the DDQ can act either as an oxidant to transform the tetrahydroquinoline **23** to quinoline **20** without formation of amine **21** or as an oxidant of amine **21** after its formation. Having found a satisfactory system, we turned our attention to the amount of $BF_3 \cdot OEt_2$ required to achieve this intramolecular imino Diels−Alder reaction in good yields. When the imine **18** with 2 equiv of DDQ in the presence of 1, 0.5, 0.2, or 0.1 equiv of $BF_3 \cdot OEt_2$ was carried out in CH_2Cl_2 at room temperature after 1 h of stirring, the chemical yield slightly decreased (72%, 63%, 54%, and 58%, respectively). In the absence of $BF_3 \cdot OEt_2$, no quinoline was formed and only decomposition of the starting material was observed.

(16) Although the imine **10** was quantitatively obtained after treatment of the reaction mixture, the yield after isolation is low because a part of the imine was decomposed during the silica gel column chromatography.

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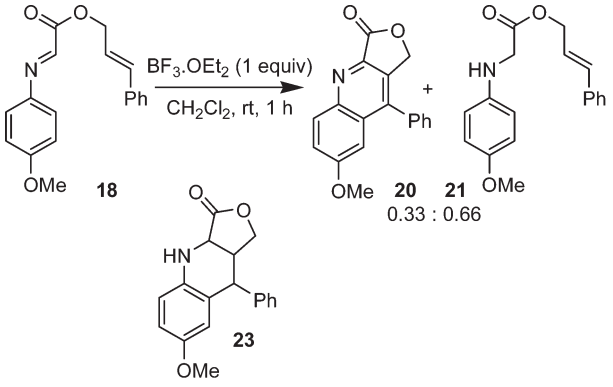
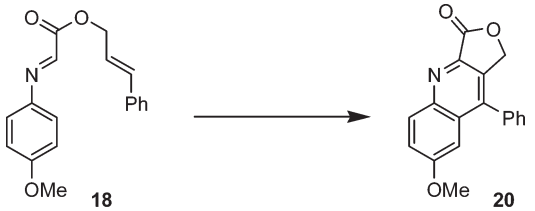
SCHEME 4. Cycloaddition Reactions



SCHEME 5. Choice of the Oxidant

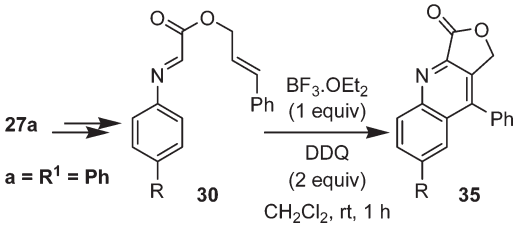


conditions	
$BF_3.OEt_2$ (1 equiv), DDQ (2 equiv), CH_2Cl_2, rt, 1 h	72%
$BF_3.OEt_2$ (1 equiv), O_2, CH_2Cl_2, rt, 1 h	23%
CAN (2.1 equiv), CH_2Cl_2, rt, 1 h	26%

Whereas the $BF_3 \cdot OEt_2$ (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 glyoxylic acid moiety was synthesized following two different routes, from the tartaric acid **25** for the alkenes' derivatives **28** and from the acryloyl chloride for alkynes' compounds **33** (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 **35** from **27** and **32**. The ^{1}H NMR spectral data were consistent with expectations for the proposed structures **30** and **34** and revealed that the products have been formed in good to quantitative conversion.

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 **28a** 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 was determined from the dicinnamyl tartrate **27a** obtained after purification in 72% yield. The intramolecular imino Diels–Alder reaction of the crude mixture of **30** was carried out in the presence of 1 equiv of $BF_3 \cdot OEt_2$ and 2 equiv of DDQ in CH_2Cl_2 at room temperature. The preparation of imine derivatives **30** works well in most cases (complete conversion) except when using the 4-nitroaniline, in which case no reaction was observed. The quinolines **35** were isolated in low to good yields; however, it appears difficult to rationalize the results based on the electronic density of the aryl group. The electron-rich imine **18** gave the best result (72% yield over 3 steps) and in the same time the electron-deficient imine **25** (R = F) afforded 65% yield in quinoline **41**.

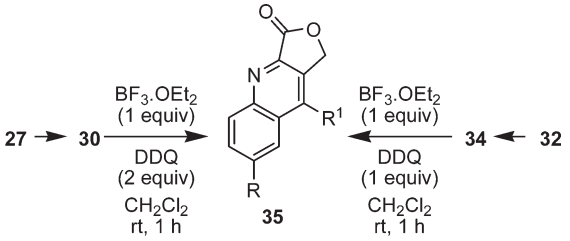
TABLE 1. Scope of the Aromatic Group



entry	R	yield, %	product
1	OMe	72	**20**
2	H	24	**36**
3	Me	47	**37**
4	NMe_2	N.R.[a]	**38**
5	Cl	57	**39**
6	CF_3	55	**40**
7	F	65	**41**
8	NO_2	N.R.[b]	**42**

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

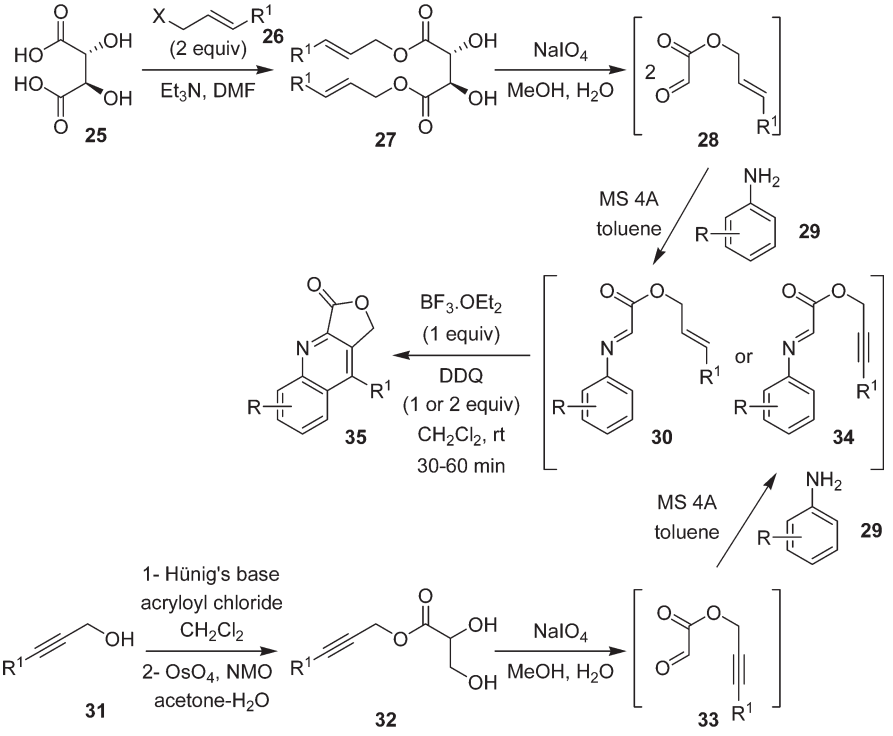
TABLE 2. Alkene vs. Alkyne



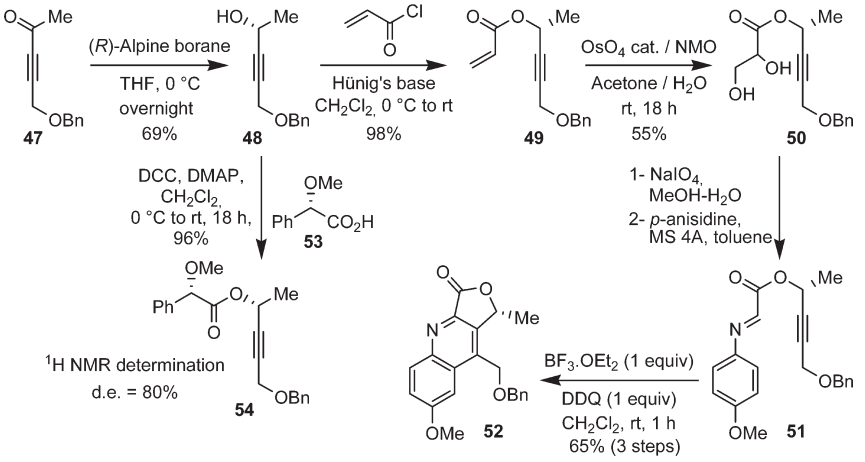
entry	R	R^1	yield, % from **27**	yield, % from **32**	product
1	H	H	N.R.[a]	N.R.[a]	**43**
2	OMe	H	15	< 5[b]	**44**
3	OMe	*n*-Pr	32	44	**45**
4	H	Ph	24	56	**36**
5	OMe	Ph	72	59	**20**
6	OMe	CH_2OBn		64	**46**

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

SCHEME 6. General Scheme of Quinoline Synthesis



SCHEME 7. Preparation of the Chiral Quinoline 52



We then compared the intramolecular cycloaddition between alkenes **30** and alkynes **34**. Various compounds were prepared as described 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 **30** or **34** into quinoline **35**. The moderate yields are due to an incomplete conversion of the diol **27** or **32** into glyoxylic derivative **28** or **33**. It is noteworthy that there is no significant difference between the alkenes' route and the alkynes' route. Because only 1 equiv of DDQ is required, it seems more interesting to use the latter.

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 **47**.[20] Enantioselective reduction of **47** with (*R*)-Alpine borane according to Brown[21] afforded cleanly the alcohol **48** with 80% ee as determined from the ^{1}H NMR after derivatization into its corresponding *O*-methylmandelic ester **54**.[22] The alkynol **48** was converted in acryloyl ester **49** and the diol **50** was isolated as a diastereomeric mixture after osmylation reaction in 55% yield. The diol **50** was converted into its glyoxylic acid derivative, which was treated with *p*-anisidine in toluene in the presence of molecular sieves to give the

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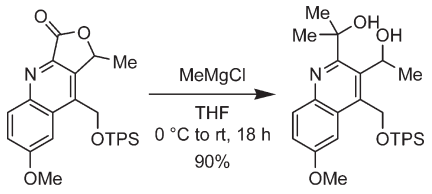
(22) (a) A partial epimerization probably occurred in the course of the formation of the mandelic ester 54. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.

SCHEME 8. Synthesis of Quinoline 56



imine **51** (Scheme 7). After imino Diels−Alder cycloaddition the quinoline **52** was isolated in 65% yield overall from the diol **50** with 89% ee as determined by HPLC.[23] To continue toward the synthesis of uncialamycin **1**, we envisage these following steps: lactone ring-opening, decarboxylation, and a diastereoselective intermolecular addition of acetylide.

Finally, to confirm the formation of the quinoline, the lactone opening of the racemic quinoline **55**[13] was carried out with an excess of methyl magnesium chloride to afford the *gem*-dimethyl alcohol **56**. Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of dichloromethane at room temperature from an ethanol/dichloromethane solution of **56**. The X-ray crystal structure analysis of **56** shows the expected quinoline core (Scheme 8).[13]

Conclusions

In summary, we have described that $BF_3 \cdot OEt_2$ in the presence of DDQ promotes the intramolecular Povarov reaction and oxidative aromatization affording substituted quinolines. The dienophile could be either an alkene or an alkyne without the yield of cyclization being affected. One equivalent of DDQ is necessary in the case of the cycloaddition reaction with the alkynes while it takes 2 equiv for the reaction with alkenes. In the absence of DDQ, the cycloaddition reaction occurs but the quinoline was obtained as a mixture with an amine, which results in 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

General Procedure for Intramolecular Imino Diels−Alder Reaction: Preparation of Quinoline 20 from 18 (Table 1, entry 1). To a 0.2 M solution of the crude imine **18** in dichloromethane under argon atmosphere at rt was added 2 equiv of dichlorodicyanoquinone and then 1 equiv of boron trifluoride diethyl etherate. 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 52 (Scheme 7). 5-(Benzyloxy)pent-3-yn-2-one (47):[24] To a solution of 1-[(prop-2-ynyloxy)methyl]-benzene (3.00 g, 20.5 mmol, 1 equiv) in tetrahydrofuran under argon atmosphere at −78 °C was added *n*-butyl lithium (2.5 M in hexanes, 9.03 mL, 22.6 mmol, 1.1 equiv). After 30 min at −78 °C *N*-acetylmorpholine (4.78 mL, 41.0 mmol, 2 equiv) was added and the reaction mixture was allowed to warm to rt overnight. The reaction was then quenched with a saturated aqueous solution of ammonium chloride. The product was extracted with ethyl acetate (3 times) and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 95:5 as eluent to obtain **47** 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 (48):[25] To a commercial solution of (*R*)-Alpine borane (0.5 M in THF, 8.50 mL, 4.25 mmol, 2 equiv) under argon atmosphere at 0 °C was added **47** (400 mg, 2.12 mmol, 1 equiv). The tetrahydrofuran was removed under reduced pressure at 0 °C and the resulting oil was stirred at rt 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 sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 8:2 as eluent to obtain **48** as a colorless oil (280 mg, 1.47 mmol, **69%**). R_f 0.2 (cyclohexane/ethyl acetate 7:3); ee 80% ; $[\alpha]^{22}_D$ +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 (br s, 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 (49): To a solution of **48** (1.00 g, 5.26 mmol, 1 equiv) and Hünig's base (2.72 mL, 15.8 mmol, 3 equiv) in 20 mL of dichloromethane at 0 °C under argon atmosphere was added acryloyl chloride (854 μL, 10.5 mmol, 2 equiv). The mixture was allowed to warm to rt overnight and quenched with a saturated aqueous solution of ammonium chloride. 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 with cyclohexane/ethyl acetate 95:5 as eluent to obtain **49** as a colorless oil (1.26 g, 5.16 mmol, **98%**). R_f 0.4 (cyclohexane/ethyl acetate 8:2); $[\alpha]^{22}_D$ +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 (50): To a mixture of **49** (1.00 g, 4.09 mmol, 1 equiv) and *N*-methylmorpholine *N*-oxide (663 mg, 4.91 mmol, 1.2 equiv) in 30 mL of

(23) Chiralpack AD-H column (5 mm, 4.6 × 250 mm) with a UV detection at 259 nm at 20 °C, eluent heptane/isopropanol = 8/2, retention times 13.08 and 15.80 min. See the Supporting Information.

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acetone/water 9:1 was added a solution of osmium tetroxide (0.5% w/v in *tert*-butyl alcohol, 2.08 mL, 0.041 mmol, 0.01 equiv). The mixture was stirred overnight at rt in the dark and was quenched with a saturated aqueous solution of sodium bisulfite. The resulting mixture was extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 1:1 as eluent to obtain **50**, 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); $[\alpha]^{22}_D$ +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 (br s, 1H), 2.56−1.82 (br s, 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 (51): To a solution of **50** (540 mg, 1.94 mmol, 1 equiv) in 10 mL of tetrahydrofuran/water 9:1 at rt was added sodium periodate (830 mg, 3.88 mmol, 2 equiv). The mixture was stirred overnight at rt 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 sodium sulfate, and concentrated under reduced pressure. To a solution of this yellow oil in 8 mL of toluene under argon atmosphere at rt was added 5 g of molecular sieves 4 Å in powder and *p*-anisidine (240 mg, 1.94 mmol, 1 equiv). The resulting mixture was stirred overnight at rt and the molecular sieves was removed by filtration. The filtrate was concentrated under reduced pressure to obtain **51** 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 (52): To a solution of crude imine **51** (682 mg, 1.94 mmol, 1 equiv) in 12 mL of dichloromethane under argon atmosphere at rt were added dichlorodicyanoquinone (440 mg, 1.94 mmol, 1 equiv) and boron trifluoride diethyl etherate (244 μL, 1.94 mmol, 1 equiv). 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 **52** 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%; $[\alpha]^{22}_D$ −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.

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Supporting Information Available: Full details of the 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.