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[9] The structure of **10a** was established by X-ray diffraction. CCDC-179112 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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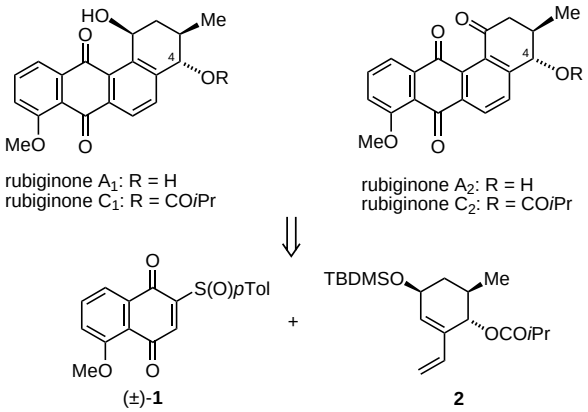
Enantioselective Total Synthesis of Angucyclinone-Type Antibiotics Rubiginones A_2 and C_2**

M. Carmen Carreño,* María Ribagorda, Álvaro Somoza, and Antonio Urbano*

The wide range of biological properties associated with the angucycline antibiotics has stimulated great interest in these compounds.[1] Among the angucyclinone subclass, rubiginones A and C are unique owing to the hydroxy function at C4 (Scheme 1). Moreover, rubiginones C_1 and C_2 represent the only natural angucyclinones that have an ester substituent at the same carbon center. Rubiginones A and C were isolated from the fermentation broth of *Streptomyces griseorubiginosus* and exhibited potentiation of vincristine-induced cytotoxicity against multidrug-resistant tumor cells.[2] Rubiginone A_2, also named fujianmycin B[3] or SNA-8073-B,[4] is claimed to be useful in the treatment of AIDS and Alzheimer's disease.[5] The absolute stereochemistry of all rubiginones has been determined by the *O*-methylmandelate method.[6]

The angularly fused tetracyclic skeleton of angucyclinones has been synthesized regioselectively by several methods, which are summarized in an excellent recent review article.[7]



Scheme 1. Retrosynthetic analysis of rubiginones A and C.

The most general strategy employed is based on the Diels – Alder reaction between a substituted naphthoquinone and a vinyl cyclohexene. Although several efficient total syntheses of angucyclinones have focused on racemic forms,[8] only a few asymmetric syntheses have been described so far.[9] Recently, we reported an asymmetric approach to angucyclinones based on the reaction of an enantiopure sulfinyl-substituted 1,4-naphthoquinone and a chiral racemic vinyl cyclohexene.[10] The sulfoxide group on the quinone framework promoted a double induction in the Diels – Alder reactions which led to the efficient kinetic resolution of the diene partner. This method has been applied to the enantioselective preparation of differently substituted natural angucyclinone derivatives.[11] Despite the numerous synthetic efforts towards this family of compounds, to the best of our knowledge no total synthesis of C4-oxygenated derivatives have been reported to date.

We describe herein the first enantioselective total synthesis of rubiginones A_2 and C_2 based on the Diels – Alder reaction of 5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**1**) and enantiopure vinyl cyclohexene **2**, which bears all the stereogenic centers present in the natural products (Scheme 1). The quinone is used in the racemic form because the role of the sulfoxide in this approach is limited to controlling the regioselectivity of the Diels – Alder reaction and facilitating the recovery of the quinone structure after the cycloaddition by pyrolytic elimination. The enantiopure diene **2** was synthesized from [(S)*S*]-[(*p*-tolylsulfinyl)methyl]-*p*-quinol (**3**) by means of a stereocontrolled conjugate addition of $AlMe_3$ as the key step (Scheme 2).

Thus, highly chemo- and diastereoselective conjugate addition of $AlMe_3$ to [(S)*S*]-**3**[12] afforded derivative **4**, which has the *R* configuration at the new C5 stereogenic center.[13] Compound **4** was further transformed into the sulfone **5** with MCPBA. Reduction of the carbonyl group of **5** with DIBAL-H provided **6**. The stereoselective reduction of **5** must be a consequence of its rigid structure and the small size of DIBAL-H, whose axial attack at the cyclohexenone ring was expected. The *S* absolute configuration at C4 of **6** was confirmed through the formation of the corresponding Mosher's esters.[14] After protection of **6** as the TBDMS derivative **7**, and elimination of methyl *p*-tolylsulfone by a Cs_2CO_3-promoted retrocondensation, ketone **8** was obtained in 87% yield. The treatment of **8** with Br_2 and Et_3N yielded

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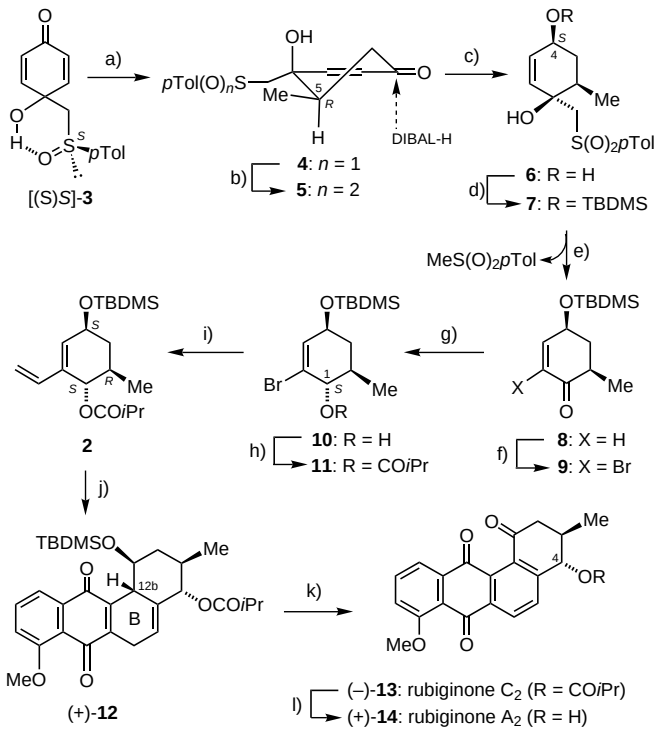

Scheme 2. Enantioselective total synthesis of rubiginones A_2 and C_2: a) $AlMe_3$, CH_2Cl_2, $-78\,^\circ C$, 4 h, 65 %; b) MCPBA, CH_2Cl_2, $0\,^\circ C$, 30 min, 96 %; c) DIBAL-H, THF, $-78\,^\circ C$, 30 min, 99 %; d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, $0\,^\circ C$, 2 h; e) Cs_2CO_3, CH_3CN, room temperature, 17 h, 87 % over two steps; f) Br_2, CCl_4, $0\,^\circ C$, then Et_3N, room temperature, 32 h, 80 %; g) $LiAlH_4$, THF, $-100\,^\circ C$, 30 min; h) *i*PrCOCl, DMAP, CH_2Cl_2, 1 h, 79 % over two steps; i) $[Pd(PPh_3)_4]$, $[CH_2{=}CHSnBu_3]$, toluene, $90\,^\circ C$, 24 h, 78 %; j) (±)-**1** (2 equiv), CH_2Cl_2, reflux, 24 h, 52 %; k) *hv*, air, room temperature, 16 h, 35 %; l) K_2CO_3, THF/MeOH, room temperature, 90 min, 91 %. MCPBA = *meta*-chloroperbenzoic acid; DIBAL-H = diisobutylaluminum hydride; TBDMSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; DMAP = 4-dimethylaminopyridine.

the α-bromoenone **9**, whose stereoselective reduction with $LiAlH_4$ at $-100\,^\circ C$ afforded (1*S*)-**10** and its 1*R* epimer (93:7). The *S* absolute configuration at C1 of the major epimer was again confirmed after transformation of **10** into the Mosher's esters.[14] Finally, protection of **10** as the isobutyrate derivative **11** and Stille coupling with tributylvinylstannane gave rise to vinyl cyclohexene **2** with the appropriate absolute configuration present at the three stereogenic centers in the natural products.

With enantiopure diene **2** in hand, we undertook the regioselective construction of the tetracyclic skeleton of the rubiginones (Scheme 2) through the Diels–Alder reaction with racemic 5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**1**).[15] After heating the mixture of **1** and **2** in CH_2Cl_2 at reflux for 24 h, we obtained the unstable tetracyclic quinone (+)-**12** as the sole diastereoisomer. Compound **12** results from the spontaneous elimination of the sulfoxide in the initially formed cycloadduct. The stereoselective formation of C12b was expected according to the preferred approach of the dienophile from the face of the diene *anti* to the bulky allylic OTBDMS substituent.[16]

Several attempts to aromatize the B ring of (+)-**12** with DDQ (2,3-dichloro-5,6-dicyano1,4-benzoquinone), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), or K_2CO_3 were unsuccessful and gave rise to complex reaction mixtures. Serendipitously, we found that the exposure of (+)-**12** to daylight under solvent-free conditions,[17] afforded **13** in 35 % yield ($[\alpha]_D^{20} = -57$ ($c = 0.5$ in $CHCl_3$)) which gave physical and spectroscopic data identical to those of natural (−)-rubiginone C_2 {$[\alpha]_D^{20} = -61$ ($c = 0.5$ in $CHCl_3$)}.[2] This unprecedented one-pot transformation involves three consecutive reactions of (+)-**12** in a very efficient way: aromatization of the B ring, deprotection of the silyl group, and oxidation of the resulting carbinol to give the corresponding benzylic ketone group. Finally, hydrolysis of the isobutyric ester at C4 of (−)-**13** with K_2CO_3/MeOH/THF afforded **14** in 91 % yield ($[\alpha]_D^{20} = +78$ ($c = 0.2$ in $CHCl_3$)), which was identical to natural (+)-rubiginone A_2.[18]

In summary, we have reported the first total enantioselective synthesis of the C4-oxygenated angucyclinones rubiginones A_2 and C_2 based on the asymmetric Diels–Alder reaction of the enantiopure vinyl cyclohexene (+)-**2** and the racemic methoxy-substituted sulfinylnaphthoquinone **1**. The successful route involved the chemo- and stereoselective addition of $AlMe_3$ to [(S)*S*]-[(*p*-tolylsulfinyl)methyl]-*p*-quinol (**3**) and the elimination of the chiral sulfoxide as methyl *p*-tolylsulfone as the key steps for the synthesis of enantiopure (1*S*,4*S*,6*R*)-**2**, which was obtained over 9 steps in 26 % overall yield. The total synthesis of natural angucyclinones (−)-**13** and (+)-**14** was completed after a cycloaddition/sulfoxide elimination process, through a practical light-induced sequence that involved partial aromatization, OTBDMS deprotection, and oxidation of derivative (+)-**12** over 11 steps from *p*-quinol **3** with > 95 % *ee* in 4.8 and 4.4 % overall yield for rubiginones C_2 and A_2, respectively.

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[18] Different values of the optical rotation of the natural product are reported in the literature: (+)-rubiginone A_2: $[\alpha]_D^{20} = +92$ ($c = 0.5$ in $CHCl_3$),[2] (+)-fujianmycin B: $[\alpha]_D^{20} = +50$ ($c = 0.176$ in $CHCl_3$),[3] and (+)-SNA-8073-B: $[\alpha]_D^{20} = +47$ ($c = 0.141$ in $CHCl_3$).[4] The enantiomeric excess of our synthetic (+)-**14** was shown to be >95% after transformation into the corresponding Mosher esters.[14]

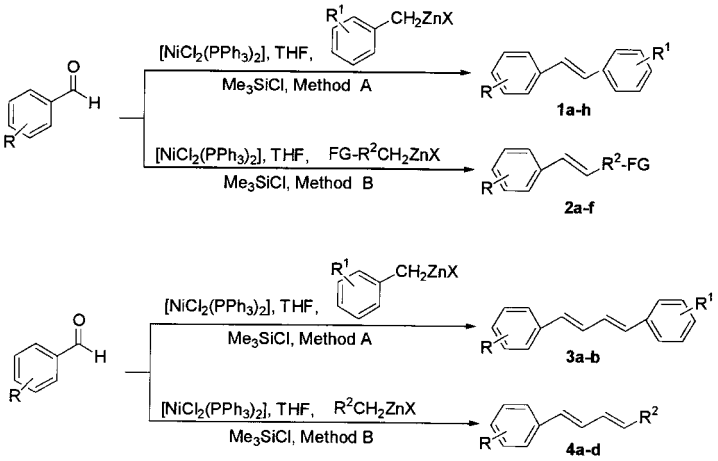
Carbon–Carbon Double-Bond Formation from the Reaction of Organozinc Reagents with Aldehydes Catalyzed by a Nickel(II) Complex**

Jin-Xian Wang,* Ying Fu, and Yulai Hu

Reactions that form carbon–carbon bonds are of the utmost importance in modern organic synthesis, and the development of new methods to form such bonds is still a formidable challenge for organic chemists. It is well known that reactions forming C=C bonds have been extensively used in the synthesis of various polyfunctional unsaturated compounds and natural products, while some applications in combinatorial chemistry have also been described. Many methods have been developed for C=C bond formation such as Wittig reactions,[1] reductive coupling of carbonyl compounds,[2] self-coupling of α-lithiated benzylic sulfones,[3] and condensation of aldehyde tosylhydrazones with stabilized carbanions.[4] More recently, new procedures for the synthesis of stilbenes have been reported, in which aldehyde tosylhydrazones were treated with benzotriazole-stabilized carbanions,[5] trimethyl borate/lithium *tert*-butoxide, trialkylboranes, and alkylboron chlorides.[6]

Organozinc complexes are powerful reagents for the formation of carbon–carbon bonds.[7] Recently, transition-metal-catalyzed coupling reactions of halides with organozinc complexes have been reported.[8] In addition, we have reported that the nitro group of 1-aryl-2-nitroethenes can be substituted by organozinc halides, using $[Ni(acac)_2]$ (acac = acetylacetonato) as a catalyst in the presence of a tertiary amine, to give 1-aryl-1-alkenes in excellent yields.[9]

The reaction of alkylzinc reagents and carbonyl compounds represents one of the most reliable methods to prepare optically active secondary alcohols.[10, 11]. Herein we show that *E*-stilbenes can be formed by the reaction of organozinc halides with aryl aldehydes in the presence of a silylating agent and using $[NiCl_2(PPh_3)_2]$ as the catalyst. To our knowledge, the formation of C=C bonds by the reaction of aldehydes and organozinc reagents, using this catalyst in the presence of chlorotrimethylsilane, is yet to be reported. Herein, we report that a number of *E*-alkenes can be obtained by this route. To investigate the scope and limitations of this new reaction for the synthesis of *E*-alkenes, various aldehydes and organozinc reagents, including some functionalized species, have been utilized as substrates (Scheme 1). The results are summarized in Table 1.



Scheme 1.

We observed that certain organozinc reagents worked best at particular reaction conditions. For the benzylic zinc halides, reactions at room temperature gave the corresponding *E*-stilbenes in good-to-excellent yields after 8 h (78–92%, entries 1–8). However, when alkylzinc iodides were used, yields of *E*-alkenes were optimized by carrying out reactions at −18 °C, and then warming to room temperature (54–89%, entries 10–15, 18–21). Both electron-withdrawing and electron-donating substituents on the phenyl ring, such as methyl, chloro, bromo, benzyloxy, hydroxy, and methoxy, are tolerated in these reactions and generally have little effect on product yield, except for 2,4-dinitrobenzaldehyde which gave no olefination product (entries 2–11 and 17). Where organo-

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