Titanium-Promoted Stereoselective Synthesis of Hydroindolones from *p*-Quinamines by Domino Conjugate Additions**

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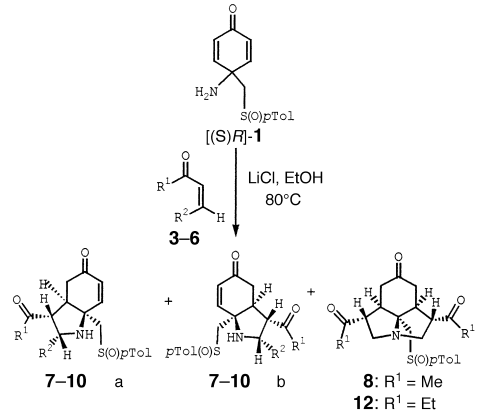
Stereocontrolled additions to conjugated double bonds included in domino processes[1] offer the opportunity to prepare structurally complex molecules from simple materials. In spite of the high synthetic potential of 4,4-disubstituted cyclohexadienones, these multifunctional materials have hardly been exploited in asymmetric synthesis.[2] Their use in domino Michael type additions for the synthesis of polycyclic compounds[3] is limited to a report from our laboratory: heterocyclic cage compounds were synthesized stereoselectively from [(S)*R*]-[(*p*-tolylsulfinyl)methyl]-*p*-quinols or the analogous *p*-quinamines[4] upon reaction with 2-trimethylsilyloxyfuran, which initially acts as a nucleophile. The ambident nature of *p*-quinamines suggested that a domino sequence could be initiated by taking advantage of the nucleophilic amino group. We report herein the reaction of *p*-quinamines **1** and **2**[4] with α,β-unsaturated ketones **3**–**6** to give rise to hydroindole or azatricyclic frameworks in a sequence of two or four stereoselective conjugate additions (Tables 1 and 2). The overall process opens an easy and convergent access to hydroindole systems, which are commonly found in alkaloids.[5]

Enantiopure [(S)*R*]-4-[(*p*-tolylsulfinyl)methyl]-*p*-quinamines **1** and **2** were synthesized from *p*-benzoquinoneimine monoacetals,[6] which are easily accessible by anodic oxidation of *N*-Boc-*p*-methoxyanilines, by addition of the α-lithiocarbanion derived from [(S)*R*]-methyl-*p*-tolylsulfoxide and hydrolysis of the acetal and *N*-Boc protecting groups.[4] The LiCl-assisted reaction of **1** with methyl vinyl ketone (**3**) afforded a mixture of hexahydroindole-5-ones **7a**, **7b**, octahydropyrroloindolone **8**, and recovered **1** (Table 1, entry 1). The formation of compounds **7** is assumed to proceed through a conjugate addition of the NH_2 group of **1** to **3**, followed by a second intramolecular 1,4 addition of the resulting enol to the cyclohexadienone from the face that contains the nitrogen substituent. This cyclization step leads to the formation of equal amounts of the two diastereomers **7a** and **7b**, since the prochiral electrophilic carbon atoms of **1** are not differentiated under these conditions. The diastereoselective formation of the C3a stereogenic center in each case was not unexpected, since the efficiency of the vicinal amino group in directing the face selectivity of conjugate additions in *p*-quinamines[4] had been previously pointed out. With an excess of enone **3** (Table 1, entry 2), the reaction proceeds via **7a** and **7b**, with a subsequent nucleophilic attack of the nitrogen atom on a second equivalent of **3**, and followed finally by a new intramolecular and stereoselective conjugate addition to the remaining cyclohexenone moiety to afford compound **8** exclusively.

Table 1. Reactions of **1** with enones in the presence of LiCl.[a]



Entry	Enone	Equiv	R^1	R^2	Products	Ratio[b] [%][c]
1	**3**	1.1	Me	H	**7a**:**7b**:**8**	30(23):30(23):10[d]
2	**3**	2	Me	H	**8**	100(52)
3	**4**	1.2	$-CH_2CH_2-$		**9a**:**9b**	50(40):50(22)
4	**5**	1.2	$-CH_2CH_2CH_2-$		**10a**:**10b**	50(27):50(16)

[a] Reagents and conditions: enone, LiCl, EtOH, 30 min, then **1**, 10 h, reflux. [b] Determined by ^1H NMR spectroscopic analysis of the crude product. [c] Yield after flash column chromatography. [d] 30% of **1** was recovered.

LiCl-promoted reaction of *p*-quinamine **1** with cycloalkenones **4** and **5** allowed the isolation of compounds **9a** and **9b** (Table 1, entry 3) and **10a** and **10b** (Table 1, entry 4), respectively. Four new stereogenic centers resulted from this domino process, with only two diastereomers being formed in each case. Although the reaction was very stereoselective, full stereocontrol and complete conversion of starting material remained a challenge. An efficient desymmetrization of the prochiral cyclohexadienone fragment had been observed in organoaluminum additions to sulfinyl-substituted *p*-quinols.[7] With this in mind, various Lewis acids ($AlMe_3$, $AlMe_2Cl$, $BF_3 \cdot OEt_2$, $TiCl_4$, $[Ti(OiPr)_4]$, $[TiCl(OiPr)_3]$, $[TiCl_2(OiPr)_2]$) were screened with *p*-quinamine **1** and cyclopentenone (**4**) as substrates.

We were delighted to observe the complete transformation of the starting materials into diastereomer **9a** (Table 2, entry 1) in the presence of $[TiCl_2(OiPr)_2]$.[8] Subsequent studies revealed that **1** reacted in a similar way with other enones. Thus, the octahydrocarbazole **10a**[9] was the major product obtained from cyclohexenone **5** (Table 2, entry 2), and hexahydroindolone **11a** resulted from ethyl vinyl ketone (**6**) (Table 2, entry 3) together with azatricyclic derivative **12** (75:25, Table 1). The use of **6** (2 equiv) led to diastereomerically pure compound **12**, which was assumed to proceed from **11a** (Table 2, entry 4). 3-Methyl-substituted *p*-quinamine [4*S*,(S)*R*]-**2a** behaved similarly in the presence of [Ti-

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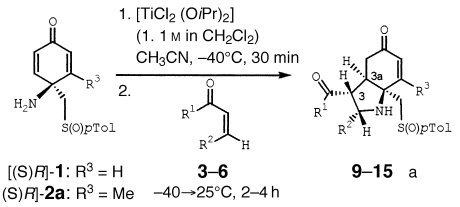
Table 2. Reactions of **1** and **2a** with α,β-unsaturated ketones in the presence of $[TiCl_2(OiPr)_2]$.

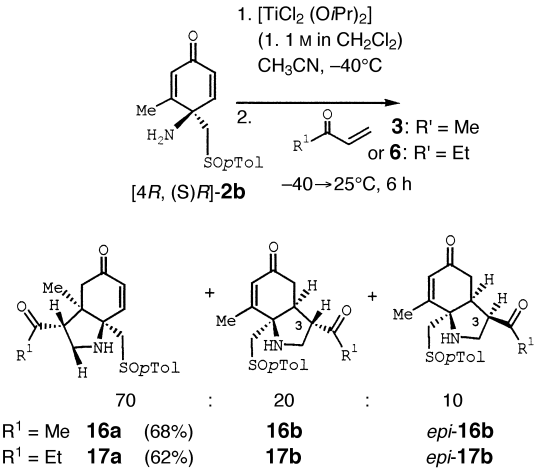


Entry	**1**–**2**	Enone	Equiv	R^1	R^2	R^3	Compound	Yield [%][a]
1	**1**	**4**	1.2	$-CH_2CH_2-$	H	H	**9a**	60
2	**1**	**5**	1.2	$-CH_2CH_2CH_2$	H	H	**10a**[b]	60
3	**1**	**6**	1.1	Et	H	H	**11a**[c]	51
4	**1**	**6**	2	Et	H	H	**12**[d]	72
5	**2a**	**6**	1.1	Et	H	Me	**13a**	54
6	**2a**	**4**	1.2	$-CH_2CH_2-$		Me	**14a**	50
7	**2a**	**5**	1.2	$CH_2CH_2CH_2$		Me	**15a**	54

[a] Yield after flash column chromatography. [b] Compound **10b** (10%) was detected in the crude reaction mixture. [c] Compound **12** (see Table 1, 25%) was detected in the crude mixture.

$Cl_2(OiPr)_2]$. Upon reaction with ethyl vinyl ketone (**6**), pure diastereomer **13a** was formed (Table 2, entry 5), and cycloalkenones **4** and **5** yielded tricyclic derivatives **14a** and **15a** (Table 2, entries 6 and 7), respectively.

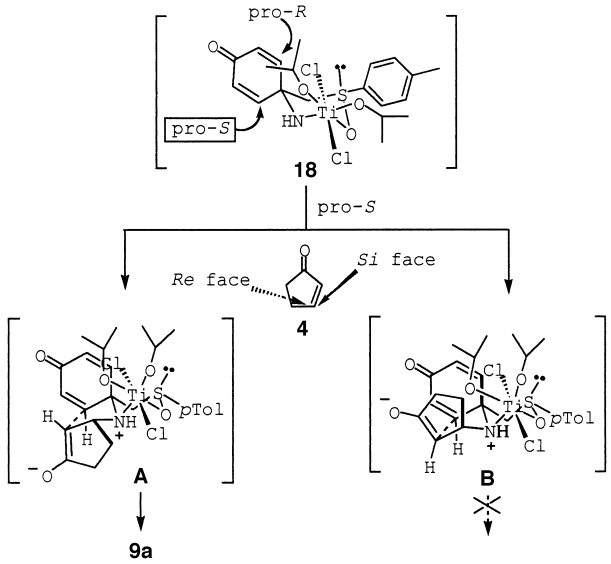
Interestingly, *p*-quinamine [4*R*,(S)*R*]-**2b** evolved under these conditions into a 70:20:10 mixture of **16a**, **16b**, and *epi*-**16b** (Scheme 1) upon reaction with methyl vinyl ketone



Scheme 1. Reaction of **2b** with acyclic enones **3** and **6** in the presence of $[TiCl_2(OiPr)_2]$.

(**3**), from which **16a** could be isolated pure in 68% yield. Compound **16a** must result from two conjugate additions; the second occurs from the less electrophilic methyl-substituted position of the cyclohexadienone moiety. Similar results were obtained in the reaction of **2b** with **6** (Scheme 1).

The remarkable level of diastereotopic bond selection observed in the cyclohexadienone moiety of **1** with $[TiCl_2(OiPr)_2]$ suggested a chelation-controlled intramolecular conjugate addition from a species such as **18** (Scheme 2). The chelate formed between the nitrogen atom of **1** and the sulfinyl oxygen atom shows a rigid bipyramidal structure,[10] with the apical Cl and the pseudoequatorial O*i*Pr groups



Scheme 2. Favored transition state for the reaction of *p*-quinamine **1** with cyclopentenone.

pointing to the spirane moiety. These substituents hinder any nucleophile from approaching the pro-*R* double bond, thereby directing the internal nucleophile to approach from the less hindered face of the pro-*S* electrophilic carbon atom (Scheme 2, transition state **A**).

The *trans* arrangement of the substituents C3/C3a of **9a** is in agreement with the most stable *trans* relationship[11] of approaching donor and acceptor in **A**. Reaction with cycloalkenones had an additional difficulty as a result of having *Re* and *Si* faces. Approach at the *Si* face (see **B**) shows a destabilizing 1,3-*syn* diaxial interaction, which would make such an attack difficult.[12]

In summary, we have disclosed Ti-promoted stereoselective domino conjugate additions of [(S)*R*]-*p*-[(*p*-tolylsulfinyl)methyl]quinamines to α,β-unsaturated ketones. Up to four new stereogenic centers are generated in a single reaction vessel when cycloalkenones are used in the reaction and up to five when two equivalents of acyclic enones used. The method allows quaternary centers to be created efficiently with a single configuration through consistent asymmetric induction.

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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**

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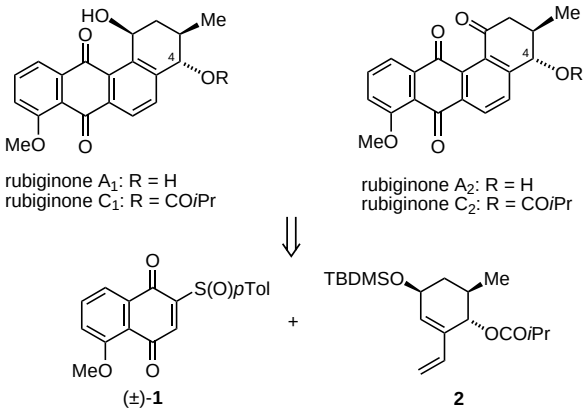
The wide range of biological properties associated with the angucycline antibiotics has stimulated great interest in these compounds.[1] Among the angucyclinone subclass, rubiginones A and C are unique owing to the hydroxy function at C4 (Scheme 1). Moreover, rubiginones C_1 and C_2 represent the only 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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