Recent Advances in the Hauser Annulation†

Dipakranjan Mal* and Pallab Pahari

Department of Chemistry, Indian Institute of Technology, Kharagpur, 721302, India

Received January 9, 2007

Contents

1. Introduction

The chemistry of aromatics traditionally centers on use of electrophilic and nucleophilic substitutions. This is largely because strategies based on such concepts are well understood and most practiced. The accompanying regiochemical problems are often disregarded, and a multistep reaction sequence is made lengthier and inefficient. Although the regiochemical problems with benzene derivatives are largely circumvented by directed metalations,[1] those with fused aromatics continue to be troublesome. A case in point is the synthesis of substituted anthraquinones by the Friedel−Crafts reaction, which is frequently accompanied by impurities arising from the Hayashi rearrangement.[2] Indeed, the past two decades have witnessed developments of many benzannulation and cyclization processes which include cobalt-mediated [2 + 2 + 2] cycloaddition[3] of acetylenes, Dötz chromium carbene complex-mediated benzannulation,[4] transition-metal(Pd, Rh, Ni, Co, etc.)-mediated cyclization,[5] Diels−Alder reactions of orthoquinodimethanes[6] and benzynes,[7] cyclobutenone rearrangement,[8] and gold- and copper-catalyzed [4 + 2] benzannulations[9] between enynal or enynone units and 2π systems.

In the late 1970s, the chemistry of well-known anticancer anthracyclines brought forth a fundamentally new benzannulation, especially when very few generalized strategies existed for the synthesis of naphthoquinones and anthraquinones. The reaction depicted in Scheme 1 is a condensation of a 3-phenylsulfonylphthalide (e.g., **1**) with a Michael acceptor (e.g., **2**) under the influence of LDA to give a 1,4-dioxygenated naphthalene derivative (e.g., **3**) in a one-pot operation.[10] Unlike the classical Robinson annulation,[11] four carbon atoms of the newly formed benzene ring in the annulation originate from the donor (**1**).

Over the years the reaction has matured and is now more widely accepted as a preferred benzannulation. The reaction can be defined as an annulation[12] (a transformation involving fusion of a new ring to a molecule via two new bonds) of a 3-(nucleofugal) benzo[*c*]furanone with an acceptor having a polarized or otherwise activated (e.g., benzyne) multiple bond to give a naphthol/naphthoquinone annulated product. In 1995, Mitchell and Russell[13] first reviewed the reaction. The present review deals with information added to the topic spanning the period 1995−2006 and missed in the first review. Although the basic chemistry behind the annulation has remained largely unaltered over the past 10 years, the reaction has witnessed significant growth in its applicability. With its use, it has been possible to assemble many important natural products like aquayamycin,[14] pentacyclic chrymutasins,[15] rugulosins,[16] and dynemicins.[17] Since it was the tenacious efforts and leadership of Prof. F. M. Hauser and his group that led to full-fledged development of the reaction, we refer to it as the "Hauser annulation" in consonance with prominent organic groups led by Suzuki,[14] Nicolaou,[16b] Swenton,[18] Julia,[19] Hassner,[20] Couladouros,[21] Brückner,[22] and Brimble.[23]

2. Background and Mechanism

That a phthalide undergoes deprotonation and carbonation at C-3 has been known since the 1960s.[24] However, the synthetic potential remained unexplored for many years. In 1977, Kraus et al.[25] showed that if substituted at C-3 with a phenylsulfanyl group, the C-3 hydrogen of isobenzofuranone (phthalide) becomes sufficiently acidic to form the corre-

† Dedicated to Professor Frank M. Hauser for his original contributions to synthetic organic chemistry.

* To whom correspondence should be addressed. Phone: +91 3222 283318. Fax: +91 3222 255303. E-mail: dmal@chem.iitkgp.ernet.in.

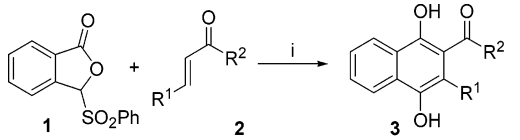
10.1021/cr068398q CCC: $65.00
Published on Web 04/20/2007

Dipakranjan Mal, born in 1952, received his B.Sc. (Hons) (1972, first class) and M.Sc. (1974, first class) degrees from the Calcutta University. After a short stint in 1976 as a CSIR Junior Research Fellow under Professor P. L. Majumder at the University College of Science, Kolkata, he proceeded to the University of Missouri at Kansas City for his Ph.D. degree (1981) on intramolecular hydrogen bonding in γ-hydroxycarboxylic acids under Professor Layton L. McCoy. During 1981–1984, he was a postdoctoral research associate with Professor Frank M. Hauser of the State University of New York, Albany. In 1984, he returned to India to accept the position of a lecturer at Bose Institute, Kolkata. Since 1987, he has been with the Department of Chemistry, Indian Institute of Technology, Kharagpur, where he is now a full professor. His research interests are focused on the development of domino strategies and total synthesis of angucyclines and anthracyclines, furocoumarins, carbazoles, and isobenzofuranone natural products. He has supervised 13 doctoral students for their Ph.D. degrees and published 70 research publications. He was a recipient of the gold medal of R. K. Mission College, Belur Math, in 1973. He received the honor certificate of Phi Kappa Phi, USA, in 1978. He is a life member of the Chemical Research Society of India.

Pallab Pahari was born in 1979 in Midnapur (W), West Bengal, India. After completing his B.Sc. (Hons) (1999, first class) and M.Sc. (2001, first class) degrees from the Vidyasagar University, he joined the group of Professor D. Mal at the Indian Institute of Technology, Kharagpur, India, as a CSIR research fellow to earn his Ph.D. degree, which will be completed in 2007. His research interests are total synthesis of angucycline antibiotics and isobenzofuranone natural products. He has published seven research publications in international journals.

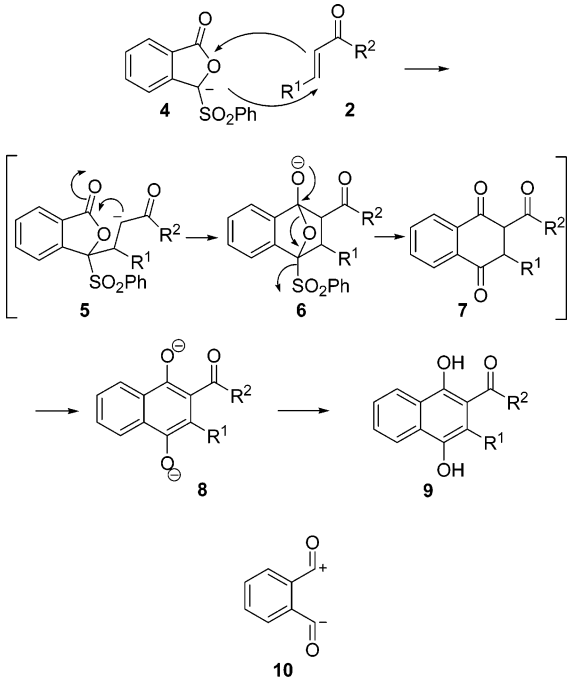
sponding carbanion which, in turn, manifests in *C*-alkylation. For instance, in reaction with Michael acceptors like ethyl crotonate and cyclohexenone, the anion gives the corresponding Michael adducts. In 1978, Hauser and Rhee[10] reported the first annulation of a 3-phenylsulfonyl-substituted isobenzofuranone **1** with various Michael acceptors constituting a fundamentally new route to highly substituted naphthalenes. In the same year Kraus et al.[26] demonstrated that 3-cyanoisobenzofuranone could be utilized as an annulating agent in place of **1**. The widespread occurrence of the 1,4-dioxygenated naphthalenes in biologically and pharmaceutically important molecules like anthracyclines led to testing of the annulation (Scheme 1) for regioselective construction of quinonoids with varying degrees of complexities.[27]

Scheme 1[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C.

Scheme 2



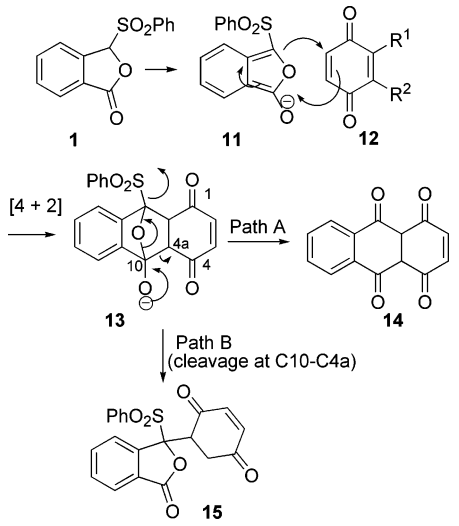
There is no systematic study on elucidation of the mechanism of the Hauser reaction, although many synthetic aspects of the reaction are reported in the literature.

The originally proposed mechanism is depicted in Scheme 2, the first step being deprotonation of phthalide **1** at C-3. The resulting anion **4** undergoes Michael addition to the acceptor **2**, and the incipient carbanion **5** undergoes intramolecular Dieckmann cyclization on the lactone carbonyl group to give **6**. Collapse of the intermediate **6** through expulsion of benzenesulfinate ion results in formation of annulated product **7**. Base-promoted tautomerization of **7** finally gives naphthoquinol **9**. In essence, the isobenzofuranone **1** is a synthetic equivalent of 1,4-dipolar synthon **10**.

The phenylsulfonyl group is thought to serve two functions: (i) it increases the acidity of the C-3 hydrogen and thus assists carbanion formation and (ii) acts as a good nucleofuge. In addition, it may be expected to facilitate the Dieckmann cyclization by contributing to the Thorpe−Ingold effect.[28]

The five-step mechanism consisting of the sequence of (i) lateral deprotonation, (ii) intermolecular Michael addition, (iii) Dieckmann condensation, (iv) elimination of benzenesulfinate anion, and (v) tautomerization is accepted by leading research groups, who utilized the reaction.[10] It is generally supported by the requirements of the reaction conditions and the structural elements that promote these

Scheme 3



reactions. It is also corroborated by isolation of the initial Michael adducts in many instances.[19] These intermediates have been submitted to final ring closure with remarkable successes to give annulated products.[19]

The most remarkable feature of the reaction is the regiochemical outcome. Attendant with Michael additions, both the addition and the ring-closure steps occur in a regiospecific manner with the Michael acceptors. If appropriately substituted phthalides and Michael acceptors are used, a single regioisomeric annulated product is formed. No cases have been found where regiochemistry has been reversed formally or informally. In reactions with a few unsymmetrical benzynes and heteroarynes, the regioselectivity is moderately affected.[29]

The reaction can, alternatively, be viewed as a synchronous [4 + 2] cycloaddition of the isobenzofuranone oxy anion **11**, the resonance structure of deprotonated **1**.The resulting cycloadduct **13** can cleave in two different competing pathways. Path A involving cleavage of the oxa bridge would give annulation product **14**. Path B involving C4a−C10 would provide 1,4-adduct **15** (Scheme 3).

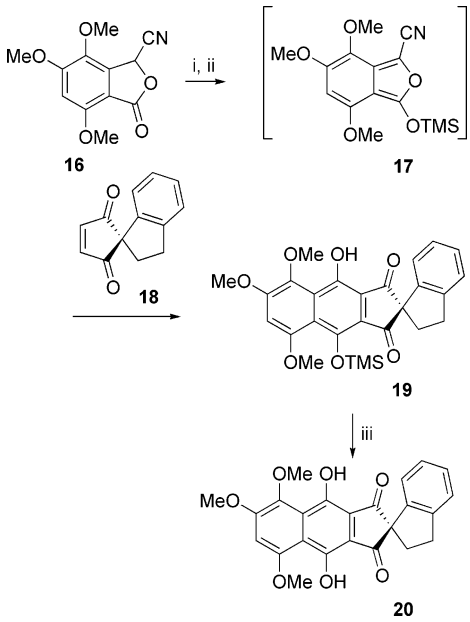
This mechanism is, in part, supported by the results with TMS-protected isobenzofuranone **17**, a structural analog of **11**, obtained from **16**.[30] Its reaction with enone **18** gave expected TMS-protected annulated product **19**. Though the isobenzofuranone **17** seemed to be unstable for isolation, its formation was indicated by analysis of the NMR spectrum (Scheme 4).

The fact that the Michael addition product **22** of the study of Lebrasseur et al.[31] could not be cyclized to give anthraquinone **23** can be interpreted comfortably by the concerted mechanism (Scheme 5).

Similarly, recent results (vide section 4.5) from the author's laboratory on successful annulations of *p*-benzoquinones with Hauser donors suggest a mechanistic dichotomy in favor of the concerted cycloaddition as the initial step.[32]

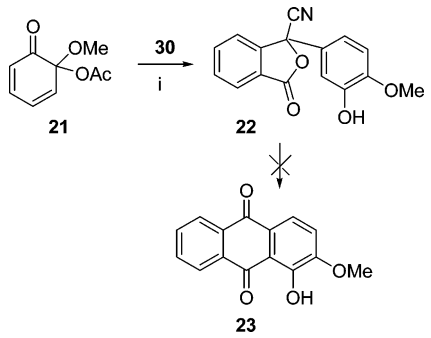
Reaction of benzocycloheptadienone **24** with isobenzofuranone **1** yielded three different annulated products **25**−**27**.[33] While formation of both **25** and **26** can be explained with the suggested concerted mechanism (Scheme 3), that of the third one, **27**, cannot be. It is a product of [4 + 4] cycloaddition, which is not thermally allowed. In view of the above background, the Hauser annulation should be attendant with duality of the mechanism (Scheme 6).

Scheme 4. Synthesis of Model Compound Related to Fredericamycin A[a]



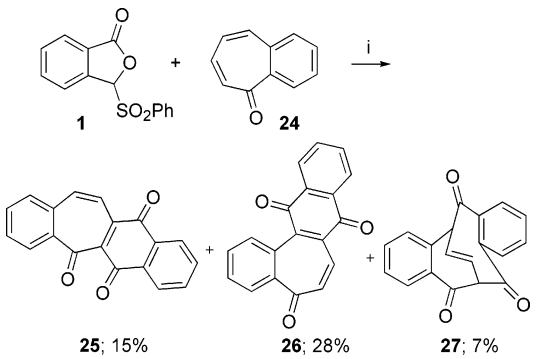
[a] Reagents and conditions: (i) *t*-BuLi, −78 °C, THF. (ii) TMSCl, −78 to 25 °C. (iii) Silica gel; 62% overall.

Scheme 5[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C.

Scheme 6[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C.

3. Types of Hauser Donors

In the original paper[10] three different phthalide donors, 3-phenylsulfonylphthalide (**1**), 3-phenylsufinylphthalide (**28**), and 3-cyanophthalide (**30**), were reportedly considered for investigations (Figure 1). Of these first-generation donors, sulfone **1** and sulfoxide **28** were studied, and the third one cyanide **30** was not synthesized due to potential hazards with its preparation. While the donor **1** worked well for the purpose, compound **28** afforded lower yields of products.

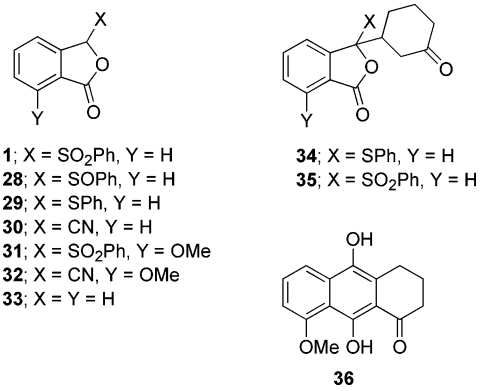


Figure 1. First-generation Hauser donors.

When a phthalide nitrile (cf. **30**) is used, it has been reported that the cyanide released during reaction adds to the Michael acceptor, and this results in lower yields of products. This problem can be circumvented using an excess of the Michael acceptor. This does not occur when the phthalide sulfone is used since sulfinate addition to the Michael acceptors does not usually occur, since this is an acid-catalyzed not a base-catalyzed reaction.

It was apparent from the study that a group serving as both an activating one and a nucleofuge was necessary at the 3 position. Such 3-substituted phthalides, capable of undergoing annulation under basic conditions, henceforth termed as Hauser donors, could be many. However, the choice of an appropriate group leading to a new variant of the Hauser donors is made on the basis of three major considerations: (i) efficacy of the reaction, (ii) ease of preparation, and (iii) safety.

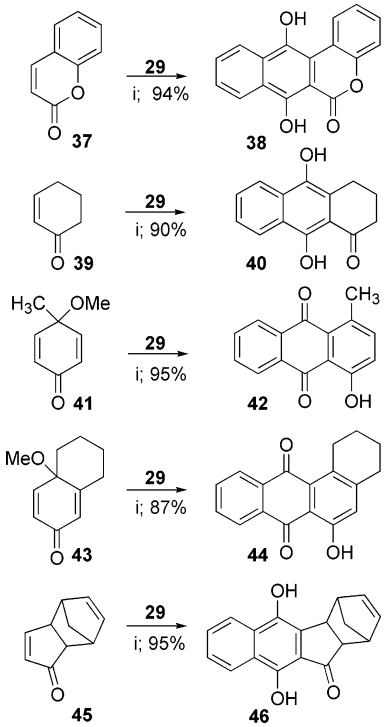
Li and Walsgrove[34] compared reactivities of the phthalide donors **1**, **29**, **31**, and **32** with a common acceptor, i.e., 2-cyclohexenone. Under their reaction conditions, understood to be LDA in THF−HMPA, both phthalide derivatives **1** and **29** provided the Michael addition products **35** and **34**, respectively, whereas reactions of **31** and **32** gave **36** (Figure 1).

Although phenylsulfanylphthalide **29** was reported not to undergo annulation with unsaturated systems, reinvestigations by Kraus et al.[35] in 1983 met with partial success when the reaction was conducted with LDA−HMPA. The yields of the reactions significantly improved when 3 equiv of potassium *tert*-butoxide (KTB) in DMSO was used and the temperature was raised to 0 °C. Subsequently, Ghorai et al.[36] conclusively demonstrated that under Hauser conditions, i.e., lithium *tert*-butoxide (LTB) in THF, phenylsulfanylphthalides (e.g., **29**) serve as excellent Hauser donors in annulation with a wide variety of acceptors (Scheme 7). In recent years, they have emerged to be the better choices in many instances.[15,22,37]

Use of phthalide-3-phosphonates (e.g., **47**, Figure 2) in the Hauser annulation was reported by Watanabe et al.[38] in 1993, and the yields of the annulations (Scheme 8) were, in most cases, excellent. Some of the known poor Michael acceptors like cyclopentenone (**56**) and methyl vinyl ketone (**58**) showed better compatibility with the Watanabe donors. Unfortunately, the difficulty in preparation of the phthalide phosphonates rendered them less attractive for future utility.

In an unprecedented report, Rho et al.[39] demonstrated that the methoxycarbonyl group behaves as a nucleofuge, in strong contrast to basic organic chemistry. Reaction of phthalide **48** (Figure 2) with methyl crotonate (**61**) under

Scheme 7. Annulation of 3-Phenylsulfanylphthalide (29) in the Presence of LTB[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C.

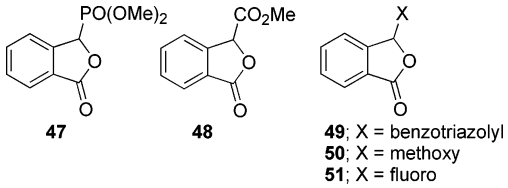
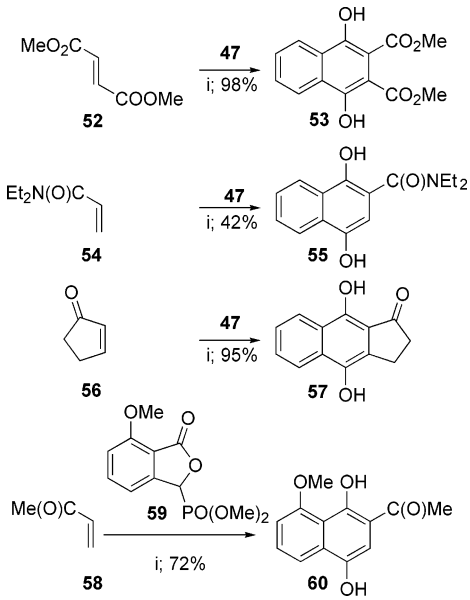


Figure 2. Second-generation Hauser donors.

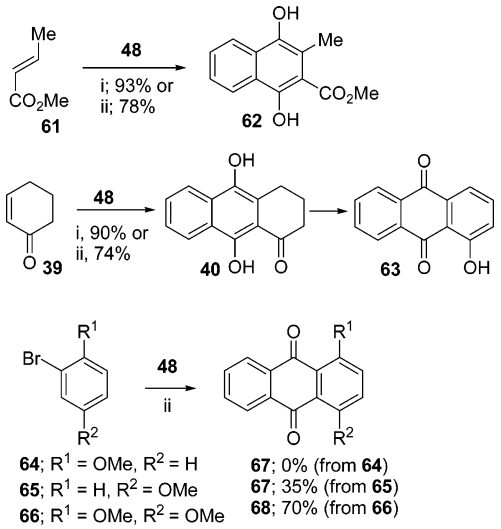
Scheme 8[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C reflux 1 h.

Hauser conditions gave the annulated product **62**. One plausible explanation could be the aromatizing driving force that resulted in expulsion of the methoxycarbonyl group. Yields of reactions with **48** were comparable to that of sulfone **1** or cyanophthalide **30**. Similarly, bromoanisoles (**65**

Scheme 9[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) LDA, THF, −78 °C.

and **66**) reacted with 3-methoxycarbonylphthalide (**48**) in the presence of LDA to give anthraquinones **67** and **68** in a one-pot operation. The driving force for such an uncommon reaction could be the stability of anthraquinone products (Scheme 9).

In 1997, Katritzky et al.[40] introduced 3-benzotriazoylphthalide (**49**) (Figure 2) as a Hauser donor. Its annulation with various open-chain Michael acceptors proceeded smoothly to give the products. Unlike the first-generation donors, it underwent annulation with unsaturated aldehydes in the presence of LDA. The products formed from the aldehydes were, however, susceptible to decomposition.

The reactivities of various 3-halophthalides toward the Hauser annulation were investigated in the authors' laboratory without any success. Fluorophthalide **51**, when reacted with LTB followed by 4-methoxy-4-methylcyclohex-2,5-dienone, provided defluorinated product, i.e., **33**.[41] A meager success was met with 3-methoxyphthalide (**50**) only for dihydroisoquinoline acceptor.[42]

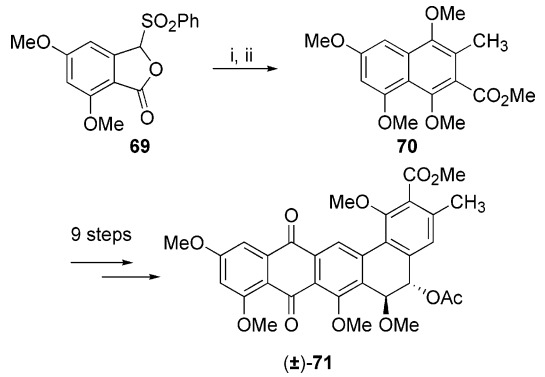
4. Reactions of the Hauser Donors

4.1. Acyclic α,β-Unsaturated Carbonyl Compounds

The discovery of the Hauser reaction began with examination of acyclic unsaturated esters and ketones. Recently, the reaction was extended to the regiospecific preparation of the hexasubstituted naphthalene derivative **70**. Reaction of dimethoxyisobenzofuranone **69** with methyl crotonate (**61**) followed by *O*-methylation regiospecifically gave annulated product **70** in 88% yield (Scheme 10). This product was utilized as an early-stage key intermediate in the total synthesis of the pradimicinone analog **71**.[43]

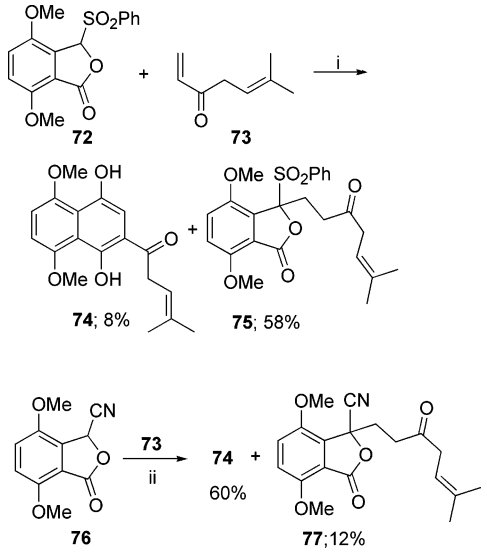
For the synthesis of shikonin (**79**), a naphthoquinone with a stereocenter in the side chain and multifarious biological activities, Couladouros et al.[21] utilized the annulation with Hauser donors **72** and **76**. While the normal annulation products were obtained with acrylonitrile and methyl acrylate, the product profile for enolizable ketones such as **73** was different. Along with desired product **74**, the corresponding Michael addition products **75** and **77** were obtained in

Scheme 10. Synthesis of Pradimicinone Analog[a]



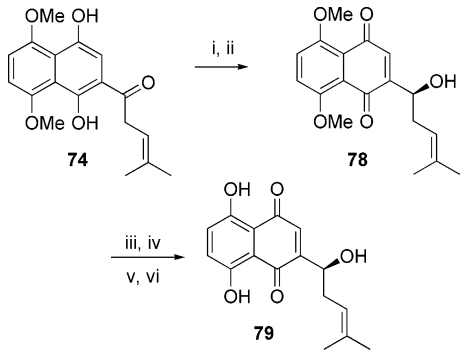
[a] Reagents and conditions: (i) methyl crotonate (**61**), LTB, THF, −78 °C. (ii) Me_2SO_4, K_2CO_3, acetone; overall 88% for two steps.

Scheme 11[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) LDA, THF, −78 °C.

Scheme 12[a]



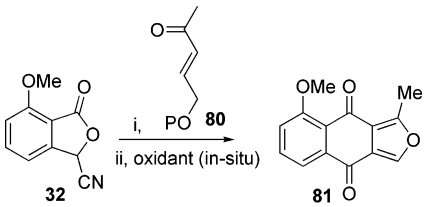
[a] Reagents and conditions: (i) (*S*)-Corey's catalyst, catechol borane. (ii) $NaBO_3 \cdot 4H_2O$, 20 h. (iii) $Na_2S_2O_4$, Et_2O/H_2O. (iv) Ac_2O, Et_3N. (v) CAN. (vi) NaOH.

substantial amounts, sulfone phthalide **72** being inferior to the cyanide **76** (Scheme 11).

The finale of the elaborate work of Couladouros et al. was an eventual multigram synthesis of shikonin (**79**) and its enantiomer alkannin (Scheme 12).

Although it is understood that any acyclic Michael acceptors would serve as Hauser acceptors, the yields of the desired condensation products may be low. In the reaction of **32** with γ-hydroxy-α,β-unsaturated ketones (e.g., **80**)

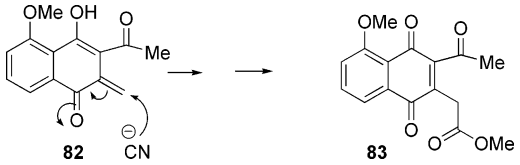
Scheme 13[a]



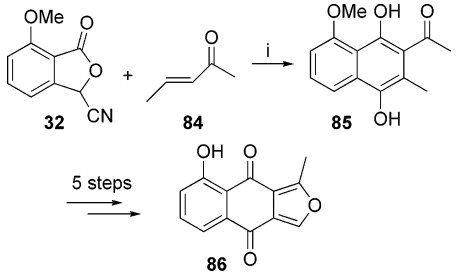
P	Oxidant	Yield
THP	CAN	9%
PMB	DDQ	30%
PMP	DDQ	0%
TBDMS	CAN	20%

[a] Reagents and conditions: (i) LDA, THF, −78 °C.

Scheme 14



Scheme 15[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C; 79%.

followed by oxidative workup, the yields of the products **81** were in the range of 0−30% (Scheme 13). As shown below, the THP- or PMP-protected Michael acceptors **80** are not at all suitable for the annulation.[44] The judicial choice of a protecting group in the γ-position of the acceptors can be the decisive factor for the improved yields.

When the reaction mixture resulting from TBDMS-protected Michael acceptor **80** was treated with ferric chloride in methanol, an unusual carbon homologated product **83** was formed in 30% yield, possibly through involvement of *o*-quinone methide intermediate **82** (Scheme 14). Formation of this byproduct could be one of the reasons for the poor yield of the naphtho[2,3-*c*]furan-4,9-dione (**81**).

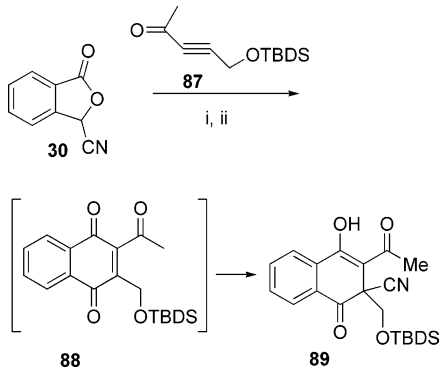
In contrast, the yield of annulation with unsubstituted pent-3-en-2-one (**84**) was remarkably higher (Scheme 15), and the product **85** was carried forward in five steps to the natural product **86**.

With an alkynone acceptor (e.g., **87**), the reaction does not stop at the desired intermediate quinone **88** and proceeds further to give the cyanide addition product **89** in an overall yield of 17% (Scheme 16).[44]

Acceptors with a substituent at the delta position undergo smooth annulation with sulfonyl phthalides, e.g., **90**. So is the result with 2,5-dienoate **93**, and the side-chain double bond does not isomerize under the reaction conditions (Scheme 17).[45]

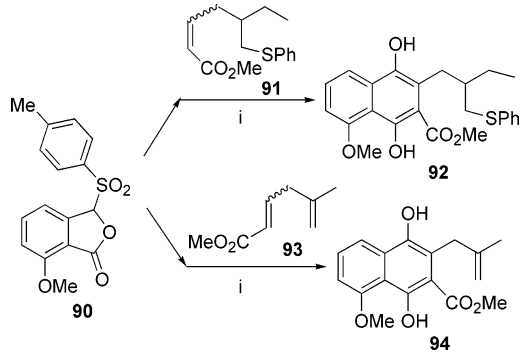
Interestingly, with an unsaturated ester having a remote carbonyl group as in **95**, the reaction does not give the normal Hauser product. Instead, it advances to include an intramolecular Claisen reaction to give a one-pot synthesis of

Scheme 16[a]



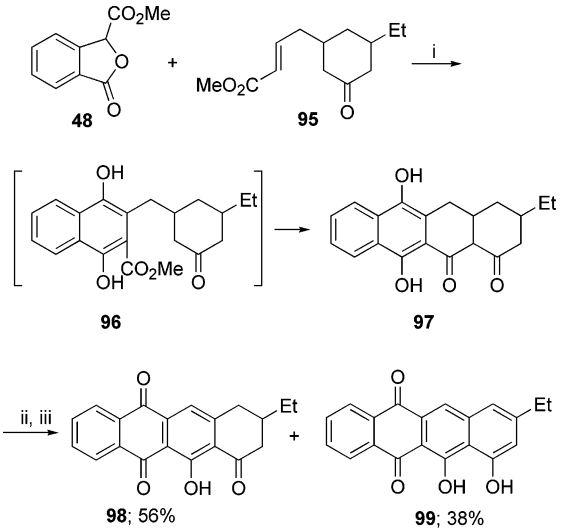
[a] Reagents and conditions: (i) LDA, THF, −78 °C. (ii) TMSCl; overall 17% for two steps.

Scheme 17[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C; 82−85%.

Scheme 18[a]



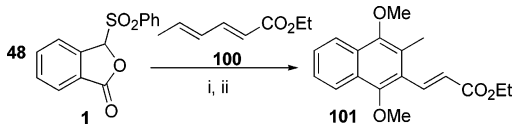
[a] Reagents and conditions: (i) LTB, THF, −78 °C to rt, 15 h; 94%. (ii) O_2, DMF, rt to 50 °C. (iii) Ag_2CO_3, celite.

naphthacenone derivative **97**, the structure of which was confirmed by its conversion to **98** and **99** (Scheme 18).[46]

When ethyl sorbate (**100**) was reacted with phthalide sulfone **1** in the presence of LDA, the condensation took place at the C-4 double bond, leaving the C-2 double bond intact, and the naphthalene **101** was obtained as the sole product, contrary to the commonly accepted notion (Scheme 19).[47]

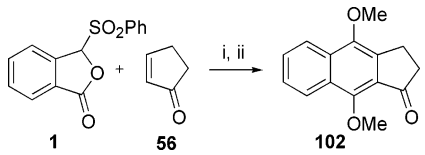
With a cross-conjugated system as in dibenzilidene acetone, the reaction proceeds to give normal mono-

Scheme 19[a]



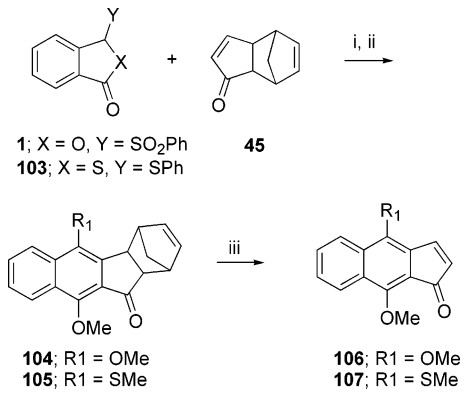
[a] Reagents and conditions: (i) LDA, THF, −78 °C. (ii) Me_2SO_4, K_2CO_3, acetone; overall 83% for two steps.

Scheme 20[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) Me_2SO_4, K_2CO_3, acetone; overall 22% for two steps.

Scheme 21[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) MeI, K_2CO_3, acetone; overall ≈ 90% for two steps. (iii) FVP; >90%.

annulation product, the second C−C double bond remaining intact.[40]

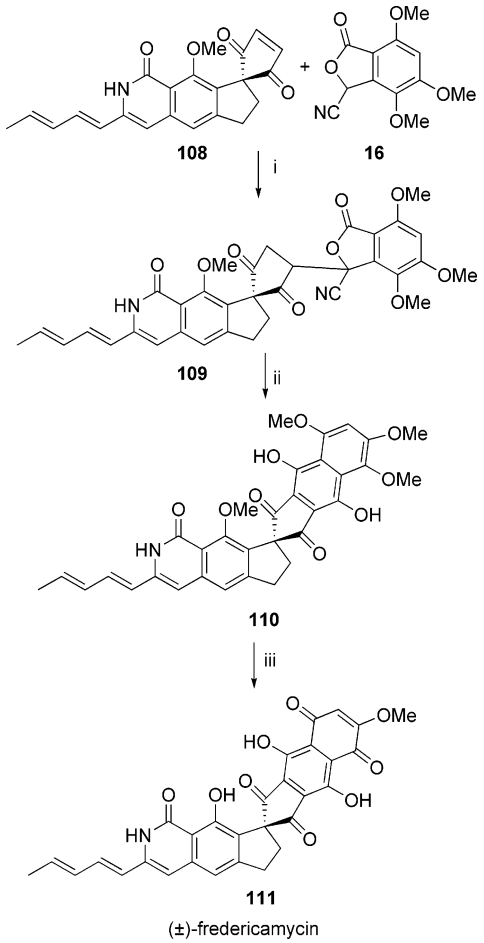
4.2. Cycloalkenones

In the context of developing a synthetic method for benz[*f*]indenones, annulation of parent cyclopentenone (**56**) with phthalide sulfone **1** was studied in the presence of LTB, and the quinol derivative **102** was obtained in a markedly low yield (22% for two steps). One of the reasons for the low yield was base-catalyzed self-condensation of cyclopentenone (Scheme 20).[48]

In contrast, the yields of annulation products were excellent when base-stable bicyclic enone **45** was used as the acceptor. Subsequent methylation of the annulated products, followed by flash vacuum pyrolysis (500 °C, 0.1 Torr), gave the corresponding benz[*f*]indenones (e.g., **106** and **107**) in excellent yields (Scheme 21).[48]

In model studies, Saint-Jalmes et al.,[19] Parker et al.,[49] and Wendt et al.[50] succeeded in assembling the benz[*f*]indene-containing spirocyclic cyclopentane unit using a Hauser annulation. Though direct condensation of the acceptor **108** and donor **16** in the presence of LDA was marginally successful, the product **110** was obtained in 78% yield in a two-step sequence (Scheme 22). Quenching the reaction at low temperature gave the Michael adduct **109**, which was isolated and then treated with NaOEt to give the annulated product **110**. It is interesting to note that protection of the isoquinolone NH was not necessary for success of the annulation. Demethylation of the condensed product **110** by

Scheme 22[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C. (ii) NaOEt, EtOH; overall 78% for two steps. (iii) BBr_3 (3 equiv), CH_2Cl_2, −78 °C to rt and then aerated for 2 days; 80%.

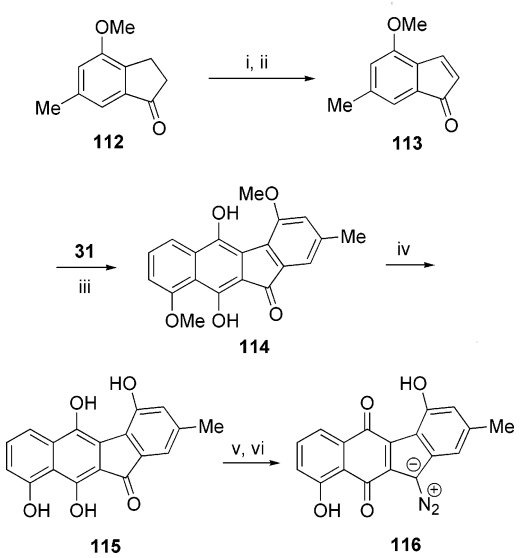
BBr_3 and air oxidation furnished (±)-fredericamycin A (**111**).[50]

The compatibility of an indenone with the Hauser annulation to give a benzo[*b*]fluorenone was first demonstrated by Mal and Hazra[51] in 1996. A similar reaction was concomitantly reported by Hauser and Zhou,[52] leading to the total synthesis of the structure proposed for prekinamycin (**116**). The yields of such annulations were consistently high (>70%). The Hauser synthesis of prekinamycin has been very useful in facilitating the mechanistic study of kinamycin antibiotics (Scheme 23).[53]

When the Hauser annulation was examined with masked cyclopentadienone **117** as a potential avenue to the synthesis of kinamycin antibiotics, a new molecular rearrangement emerged to form uncommon cyclopent[*a*]anthraquinones (e.g., **119**). The initial annulated product of **1** and **117** on DDQ oxidation provided pentacyclic compound **118**. This, on thermolysis in refluxing 1,2-dichlorobenzene, underwent tandem Cope-cheletropic reaction to give **119** in 83% yield. This rearrangement was also observed with the CH_2-bridged analog of **117** (Scheme 24).[54]

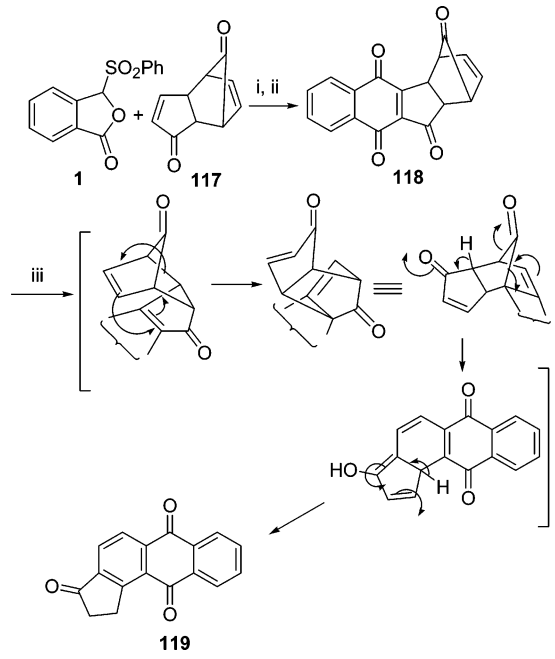
Cyclohexenones are recognized Hauser acceptors for the direct synthesis of 9,10-dihydroxyanthracenones, which have proved to be very good precursors for 9,10-anthraquinones. A number of oxidants, such as, NBS/acetone,[55a] O_2/DMF,[55b] O_2/Co−salcomine,[55c] and Ag_2CO_3−celite/Et_3N,[55d] have been used for accessing the latter from the former. Recently, the Hauser annulation of 4,4-dimethylcyclohex-2-enone (**120**)

Scheme 23. Hauser Synthesis of Prekinamycin[a]



[a] Reagents and conditions: (i) TMSTf, Et_3N. (ii) $Pd(OAc)_2$; overall 75% for two steps. (iii) LTB, THF, −78 °C; 73%. (iv) BBr_3. (v) N_2H_4, EtOH. (vi) Ag_2CO_3, celite (yields of last three steps are not specified).

Scheme 24[a]

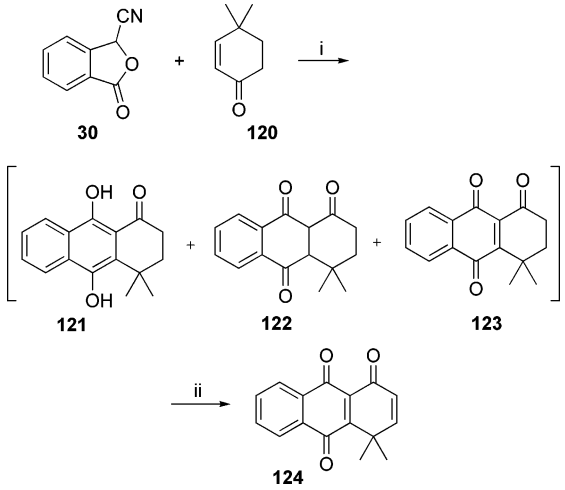


[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) DDQ, benzene, reflux. (iii) 1,2-Dichlorobenzene, reflux; overall 83% for three steps.

was examined (Scheme 25).[56] Its annulation with **30** gave a mixture of **121**, **122**, and **123** with **122** being the major product. The mixture without separation was oxidized to give naturally occurring quinone **124** in an overall 84% yield, essentially constituting a single-step synthesis. The success with **120** is clear evidence that the *gem*-dimethyl groups do not cause any neopentyl steric hindrance to the annulation, and synthesis of a quinonoid can be abbreviated by use of Hauser annulation.

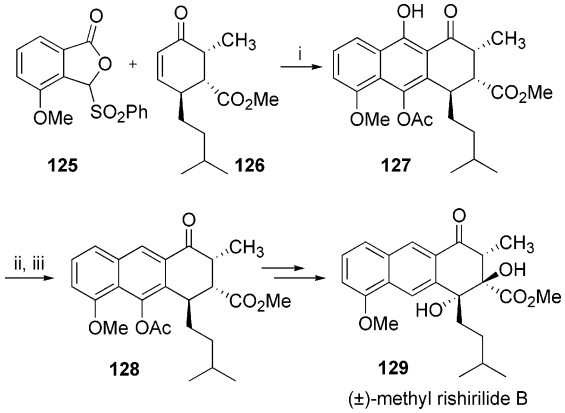
Total synthesis of (±)-methyl rishirilide B (**129**) (Scheme 26) clearly demonstrates the versatility of the Hauser annulation. A 4,5,6-trisubstituted cyclohexenone **126** could be annulated with phthalide sulfone **125** in good yield.[57] Apparently, no stereomutation was observed during the annulation. Partial deoxygenation of anthracenones **127**

Scheme 25[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C, $ZnCl_2$. (ii) DDQ, benzene, reflux; overall 84% for two steps.

Scheme 26. Hauser (±)-Methyl Rishirilide Synthesis[a]



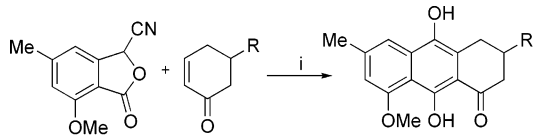
[a] Reagents and conditions: (i) LTB, THF, −78 °C, Ac_2O; 81%. (ii) NaH, Tf_2O; 51%. (iii) Pd−C/H_2; 75%.

without affecting the carbonyl carbon was performed by catalytic hydrogenation, giving **128.** This was converted to (±)-methyl rishirilide B (**129**) in six steps.

The work of Snider et al.[16a] and Nicolaou et al.[16b] on cytoskyrins advanced the chemistry of cytoskyrins and rugulosins. This has been possible through convenient access to the hydroxyanthracenones by Hauser annulations between cyanophthalides and cyclohexenones, which have been quite extensively studied in the past in the context of anthracycline syntheses. Snider's work on annulation between the cyanophthalide **130** and enones **131**−**134** in the presence of KTB and DMSO or THF showed that the yields of the annulations can vary with the nature of the R group at C-5 in the cyclohexenone acceptors. For 5-dimethylphenylsilyl derivative **131**, the yields varied from 10% to 60%. In the case of *O*-benzyl derivative **132**, there was no reaction at all and the cyclohexenone **132** was destroyed through elimination of benzyl alcohol. In the case of 5-methyl- and 5-acetoxymethyl-2-cyclohexenone **133** and **134**, the reaction proceeded smoothly to give the corresponding annulated products **137** and **138**, respectively, in moderate yields (Scheme 27). These anthracenones were finally converted to the rugulosin analogs by $Pb(OAc)_4$−pyridine-mediated dimerization.

This trend of reactivity of cyclohexenones was also observed with dimethoxy isobenzofuranones (e.g., **139**),

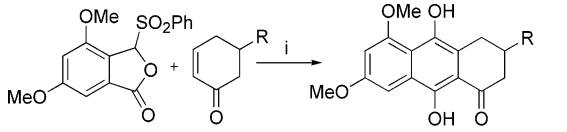
Scheme 27[a]



130 **131**; R = $SiPhMe_2$ **135**; R = $SiPhMe_2$; 10-60%
132; R = OBn **136**; R = OBn; 0%
133; R = Me **137**; R = Me; > 48%
134; R = CH_2OAc **138**; R = CH_2OAc; > 40%

[a] Reagents and conditions: (i) KTB, DMSO or THF, −78 °C.

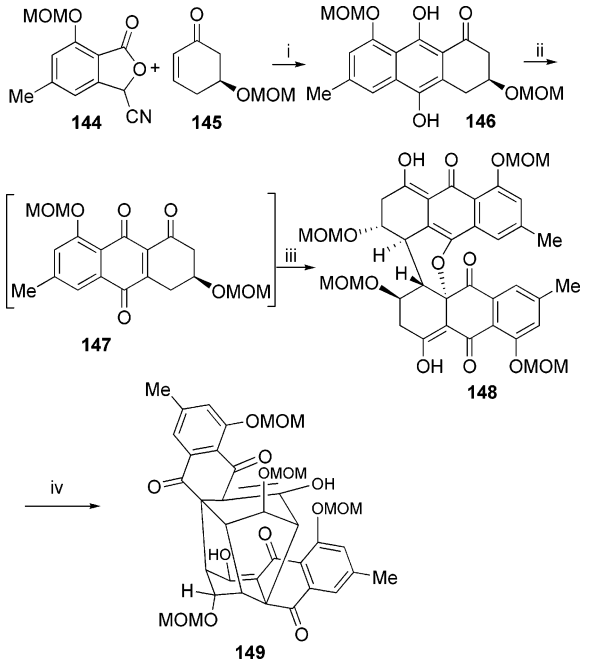
Scheme 28[a]



139 **39**; R = H **141**; R = H; 23%
134; R = CH_2OAc **142**; R = CH_2OAc; 29%
140; R = CO_2Me **143**; R = CO_2Me; 10-50%

[a] Reagents and conditions: (i) LTB, THF, −60 °C.

Scheme 29. Nicolaou Synthesis of Rugulosin[a]



144 **145** **146** **147** **148** **149**

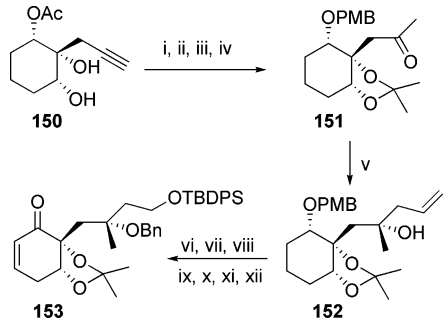
[a] Reagents and conditions: (i) LHMDS, THF, −78 °C. (ii) MnO_2, oxidation; overall 32% for two steps. (iii) enolization, dimerization. (iv) MnO_2, Et_3N (yields not reported).

indicating that nuclear methoxy substituents in isobenzofuranones have an important role in the efficiency of the reactions (Scheme 28).[58]

Nicolaou et al.[16c,d] showed that the *O*-MOM-substituted cyclohexenone **145**, unlike the *O*-benzyl derivative **132**, smoothly underwent annulation with cyanophthalide **144** to give the corresponding anthradihydroquinone **146**. Without any purification, this anthracenone was subjected to oxidative dimerization by MnO_2. The initial dimerization product **148** was further isomerized with Et_3N to give the rugulosin derivative **149** through a cascade of Michael additions (Scheme 29).

With 6-methoxy-2-cyclohexenone, the annulations of different phthalide sulfones are remarkably high yielding. Upon oxygen bubbling in DMF at 110 °C, the annulation products transform to 1,2-dihydroxyanthraquinones in >85% yields, which were utilized for the synthesis of morindaparvin A derivatives.[59]

Scheme 30[a]



150 **151** **153** **152**

[a] Reagents and conditions: (i) (a) CH_2=C(OMe)Me, TsOH, benzene, 30 min and (b) K_2CO_3, MeOH, 45 min; 97% in two steps. (ii) PMBCl, NaH, DMF, 0 °C, 2 h; 92%. (iii) H_2, quinoline, Lindlar's catalyst, hexane, 70 min; 97%. (iv) $Hg(OAc)_2$, MeOH, 1 h, then $PdCl_2$, LiCl, $CuCl_2$, 30 min; 80%. (v) CH_2=$CHCH_2ZnBr$, Et_2O, −78 °C; 89%. (vi) BnBr, KH, cat. $(n\text{-}Bu)_4NI$, DMF, 0 °C, 1.5 h; 98%. (vii) O_3, MeOH, −78 °C, then $NaBH_4$, 0 °C, 1 h; 78%. (viii) TBDPSCl, imidazole, DMF, 25 min; 98%. (ix) DDQ, CH_2Cl_2, H_2O, 0 °C, 30 min; 98%. (x) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 50 min; 94%. (xi) KHMDS, THF, −78 to −40 °C, 30 min, then CH_2=$CHCH_2OCOCl$, −78 °C; 100%. (xii) $Pd(OAc)_2$, MeCN, 15 h; 82%.

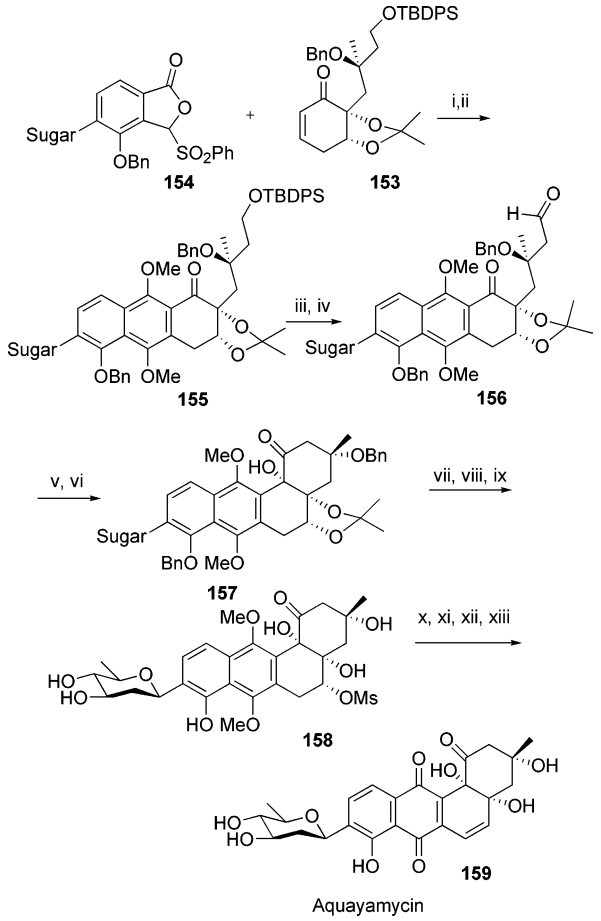
The Hauser annulation has greatly simplified the synthesis of aquayamycin (**159**), the first ever isolated *C*-glycosidic angucycline. Combination of the reaction with an intramolecular pinacol coupling led to completion of the first total synthesis of aquayamycin by Matsumoto et al.[14] in 2000. It is to be noted that oxygenated angucyclines are very sensitive to acids, bases, heat, and light.

Cyclohexenone derivative **153** (Scheme 30) was prepared in 13 steps from enantiomerically pure cyclohexane-1,2,3-triol **150**.[60] Reaction of allylzinc with **151** produced the enantiomerically pure alcohol **152**. The double bond at C2 of **153** was introduced by the Tsuji procedure.[61]

Phthalide sulfone **154**, prepared in more than 10 steps according to the sequence discussed in Scheme 79, was condensed with highly oxygenated cyclohexenone **153** to give the corresponding hydroquinone. This was, without purification, converted to its *O*-dimethyl derivative **155**, the overall yield for the two steps being 73%. The key aldehyde **156** was prepared from **155** by Swern oxidation preceded by removal of the TBDPS group. Pedersen intramolecular pinacol coupling of **156** using VCl_3·THF and Zn followed by Swern oxidation of the pinacol product provided the tetracyclic intermediate **157**. This was then converted to **158** in three steps: (i) acetonide hydrolysis, (ii) mesylate formation of a secondary alcohol group, and (iii) reductive removal of benzyl groups. Selective deprotection of the C-8 phenolic group of **158** by benzyl bromide and Cs_2CO_3 and subsequent CAN oxidation furnished the quinone derivative. Reductive debenzylation followed by elimination of the mesyl group with *i*-Pr_2NEt completed the total synthesis of aquayamycin (**159**), the overall yield being 21% for 13 steps from sulfone phthalide **154** and cyclohexenone derivative **153** (Scheme 31).[14]

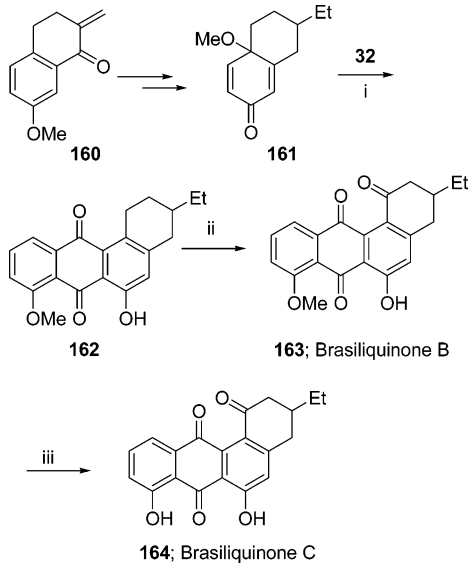
Mal and Roy[62] reported that the fused cyclohexadienones could readily be annulated with cyanophthalides to give the corresponding 1,2,3,4-tetrahydrobenz[*a*]anthraquinones. The authors applied this methodology to the total synthesis of brasiliquinone B (**163**) and C (**164**), in which Krohn photooxidation was used as a key step in generating the keto function at C-1 (Scheme 32). Commercially available

Scheme 31. Total Synthesis of Aquayamycin[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) Me_2SO_4, K_2CO_3, acetone; 73% in two steps. (iii) HF·$(Py)_n$, THF, rt; 91%. (iv) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 0 °C; 90%. (v) VCl_3·$(THF)_3$, Zn, DMF; 89%. (vi) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 0 °C; 90%. (vii) 5% aq. H_2SO_4; 96%. (viii) MsCl, DMAP, Py; 100%. (ix) H_2, 10% Pd−C. (x) BnBr, Cs_2CO_3; 79% in two steps. (xi) CAN, CH_3CN, rt. (xii) H_2, 5% Pd−C, then air. (xiii) (*i*-Pr)$_2$NEt, 1,4-dioxane; overall 58% for three steps.

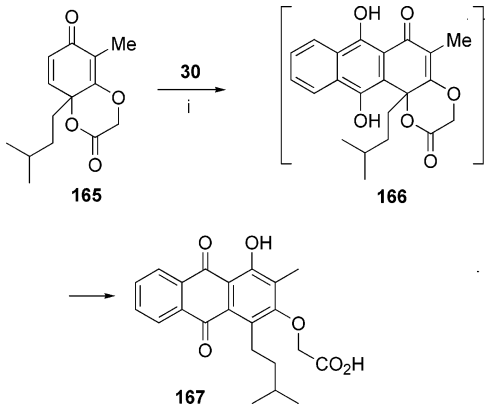
Scheme 32[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C; 92%. (ii) O_2, *hν*; 76%. (iii) $AlCl_3$, rt; 87%.

7-methoxy-α-tetralone was used for the preparation of decalenone **160**. This was elaborated to **161** through use of

Scheme 33[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C; 82%.

(i) cuprous-iodide-promoted conjugate addition of CH_3MgI, (ii) reduction with hydrazine−KOH in ethylene glycol, (iii) demethylation, and (iv) PIDA oxidation of the prepared naphthol in methanol. The naphthalenone **161**, obtained as a 1:1 mixture of diastereomers, was treated with the anion of 7-methoxycyanophthalide (**32**) to give the tetracyclic compound **162** in 92% yield. Installation of the keto functionality at C1 by aerial photo-oxidation of **162** completed the total synthesis of brasiliquinone B (**163**). $AlCl_3$-induced demethylation of **163** furnished brasiliquinone C (**164**).

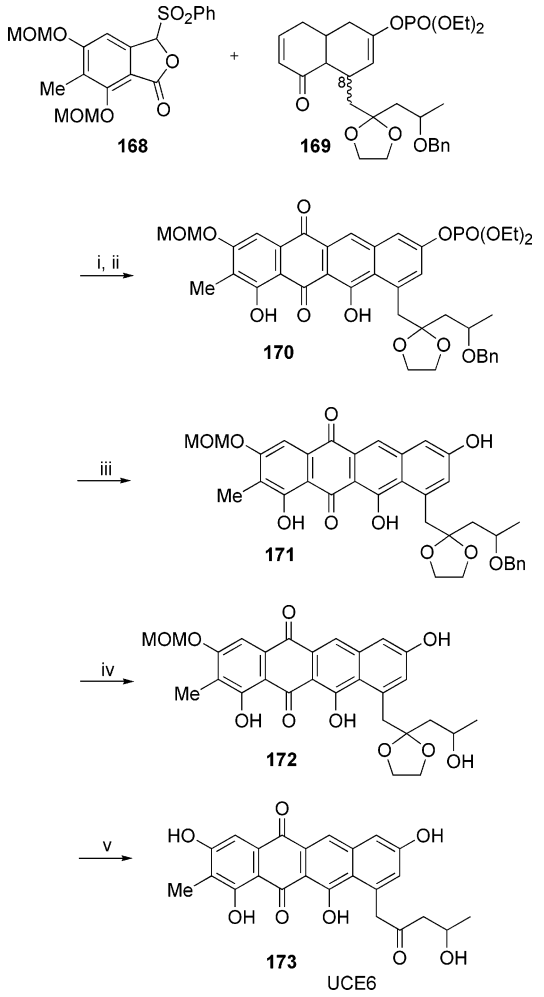
Wang et al.[63] investigated the annulation of oxygenated cyclohexadienone **165** in their study on rishirilide. Reaction of **165** with sulfonyl phthalide **1** did not provide any annulated product, possibly due to the steric hindrance exerted by two substituents at the para position. However, cyanophthalide **30** worked well to give **167** through the anticipated dihydroxy intermediate. The much desired intermediate **166** with a stereocenter could not be isolated (Scheme 33) due to facile elimination of the tertiary lactone oxygen.

In the pioneering work of Hauser and Mal,[64] it is amply demonstrated that decalenones can be annulated to give naphthacenedione of 11-deoxyanthracyclines in which A rings are nonaromatic. Tatsuta et al.[65] showed that a similar strategy could be applicable to the synthesis of the naphthacenedione skeleton of UCE6 (**173**), an antitumor antibiotic that contains an aromatic A ring. They accomplished the total synthesis in a regiospecific manner in 24 steps. The initial annulated product of **168** and **169** on dehydrogenation with palladized carbon furnished the tetracyclic product **170**, the enol phosphate functionality remaining intact. It is also to be noted that the cis stereochemistry of the ring juncture and that of C-8 of the decalenone **169** did not affect the yield of the product **170** (Scheme 34).

Hauser and Prasanna[66a] and Rho et al.[66b,c] synthesized naphthacenedione **176** using naphthalenone derivative **174** as the acceptor. The annulation formed intermediate **175**, which upon oxidation with oxygen in hot DMF afforded naphthacenedione **176** in 85% yield (Scheme 35). The 10-oxo-rhodomycinone derivative **177** was then synthesized from this naphthacenedione by several functional-group manipulations such as epoxidation, rearrangement of epoxide, base-catalyzed dihydroxylation, and isolation through boronate formation.[66b] Similar routes also provided 10-fluoroanthracyclines.[66c]

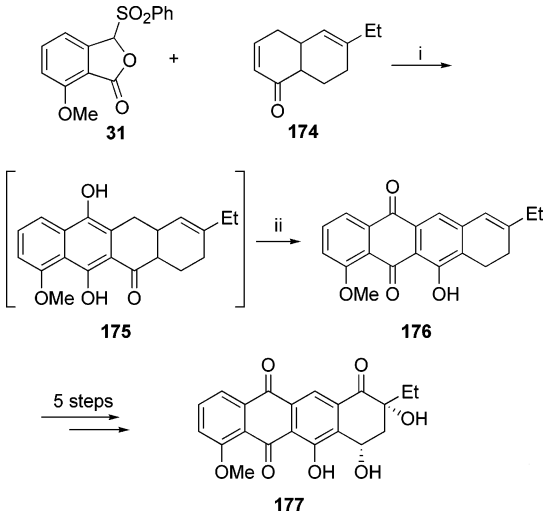
Although the simplest 2-cycloheptenone was never investigated, benzocycloheptenones were shown to undergo

Scheme 34. Tatsuta Synthesis of UCE6[a]



[a] Reagents and conditions: (i) LHMDS, THF, −78 °C. (ii) Pd−C, BnOMe, 110 °C; 64% in two steps. (iii) KTB; 85%. (iv) H_2/Pd(OH)$_2$−C, dioxane; 90%. (v) $LiBF_4$; 76%.

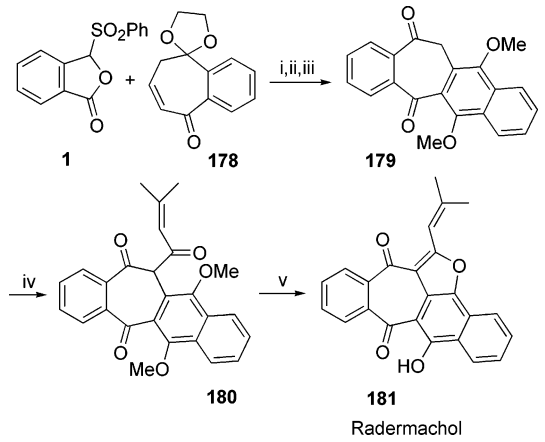
Scheme 35. Synthesis of 11-Deoxy-4-methoxy-10-oxo-β-rhodomycinone[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C to reflux. (ii) O_2, DMF; overall 84% for two steps.

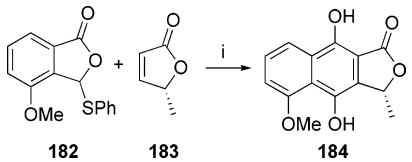
Hauser annulation with phthalide sulfone **1**. In achieving the total synthesis of radermachol (**181**), Hauser and Yin[33] reported annulation of **178** with **1** to give **179** after methylation by a nonconventional method and PPTS-catalyzed hydrolysis. An acyclic version of the Friedel−Crafts reaction provided **180**. This was cyclized through demethylation with TMSI to give radermachol (**181**) (Scheme 36).

Scheme 36. Synthesis of Radermachol[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) TBAF, MeI, DMF; overall 75% for two steps. (iii) PPTA, acetone/H_2O; 97%. (iv) $AlCl_3$, dimethyl acryloyl chloride; 13%. (v) TMSI, MeOH, PTSA (yield not specified).

Scheme 37[a]



[a] Reagents and conditions: (i) THF/DMSO (1:1), MeLi, 0 °C; 56%, 96% ee.

4.3. Furanones and Pyranones

Braukmuller and Brückner[22] recently employed optically active butenolides in the Hauser annulation to accomplish total synthesis of eleutherol in moderate yield without any stereomutation. Thus, naphtho-γ-lactone **184** was synthesized in an enantiospecific manner by the Hauser annulation between phenylsulfanylphthalide **182** and furanone **183**. Unlike common reported procedures, they used dimsyl−Li (in 3:2 THF/DMSO) in 0 °C for deprotonation of phthalide **182**. The enantiomeric purity of **184** was excellent (96%), though the chemical yield was comparatively low (Scheme 37).

The suitability of 3-pyrones as Hauser acceptors was almost simultaneously recognized by Freskos and Swenton[67a] and Tatsuta et al.[67b] in 1985, and regiospecific syntheses of many naphthopyranone natural products were achieved. Tatsuta et al.,[68] Hoffmann and Lackner,[69] and Nomura et al.[70] completed the chiral synthesis of nanoamycin (**185**), kalafungin (**186**), medermycin (**188**), and granaticin (**189**), the Hauser annulation being the key common element of the strategies (Figure 3). Also common to all syntheses were the carbohydrate-based Michael acceptors. The De Kimpe research group, a pioneer in the field of the synthesis of naphthopyranone antibiotics, recently found Hauser annulation to be superior to the existing methodologies and accomplished a short and efficient synthesis (Scheme 38) of pentalongnin (**192**) from pyrone **190** via naphthoquinol **191**.[71]

Swenton et al.[72a] and Deshpande et al.[72b] utilized this strategy for the enantioselective total synthesis of hongconin

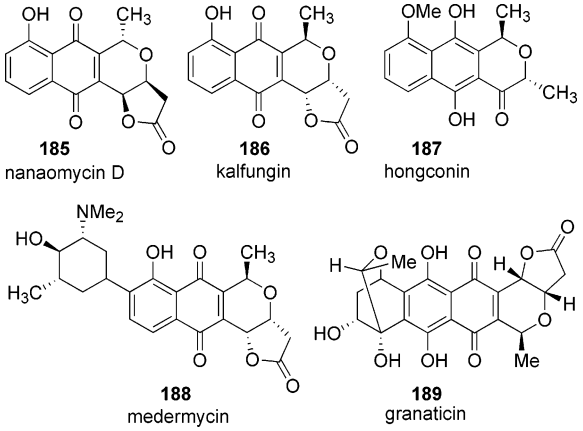
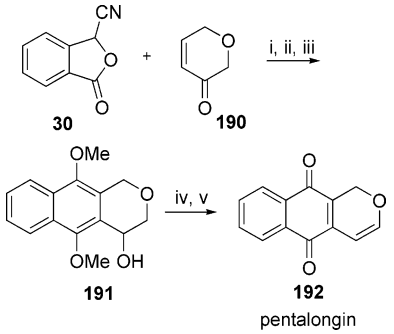


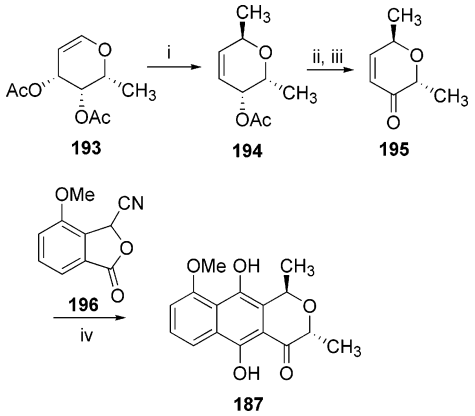
Figure 3.

Scheme 38. Synthesis of Pentalongin[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C, LiCl (cat.). (ii) Me_2SO_4, K_2CO_3. (iii) $NaBH_4$; 25% in three steps. (iv) CAN; 95%. (v) PTSA; 37%.

Scheme 39. Baker Synthesis of Hongconin[a]

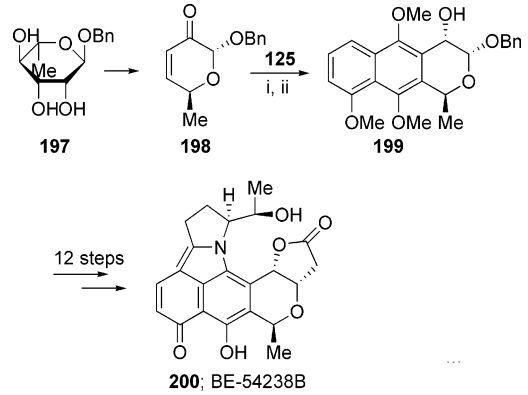


[a] Reagents and conditions: (i) $AlMe_3$, $TiCl_4$; 85%. (ii) NH_3, MeOH. (iii) PDC−Ac_2O; 60% in two steps. (iv) LTB, THF, −78 °C, LiCl (cat.); ~65%.

(**187**), a pyranonaphthoquinone with antianginal activity. Baker's synthesis is concise and more versatile than that of Swenton. The difference between the two is that the Hauser reaction is the last step in the former, thus avoiding the peripheral synthetic operations. No epimerization of the chiral centers was observed during the annulation. Pyranone **195**, prepared from glycal **193** in three steps through **194**, was annulated with **196** to give hongconin **187** in 65% yield (Scheme 39).

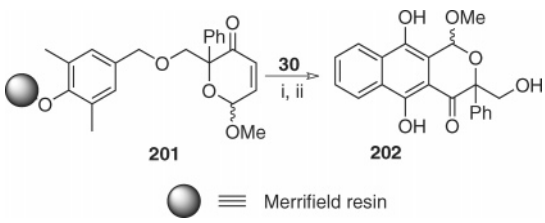
More recently, Tatsuta et al.[73] accomplished a total synthesis of the more complex naphthopyranone antitumor agent BE-54238B (**200**) utilizing a carbohydrate-derived pyranone **198**. As shown in Scheme 40, the reaction between

Scheme 40. Synthesis of BE-54238B[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) Me_2SO_4, K_2CO_3; overall 83% for two steps.

Scheme 41[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C. (ii) TFA; overall 80% for two steps.

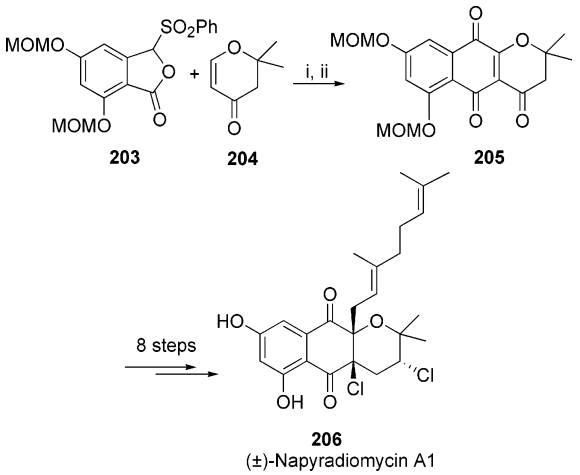
4-methoxy-3-phenylsulfonylphthalide (**125**) and pyranone **198** gave product **199** in greater than 83% yield in an early stage of a 15-step sequence.

One of the unique advancements of the Hauser annulation can be found in the solid-phase synthesis of naphthopyranones from the library of 2*H*-3-pyran-3(6*H*)-ones linked to Merrifield resin through a hydroxybenzyl alcohol linker.[74] Reaction of cyanophthalide (**30**) with polymer-supported pyranones **201** followed by TFA treatment yielded naphthopyranone **202** in 80% yield, which is comparable to those of solution-phase synthesis (Scheme 41).

In the recent past, Tatsuta et al.[75] showed that an unsaturated 4-pyrone can also be a Hauser acceptor. They could complete the first total synthesis of (±)-napyradiomycin A1 (**206**) using the Hauser reaction as the key step (Scheme 42). The yield of the annulation was fairly good (>64%) compared to that with a 4*H*-benzopyranone.[76] The intermediate **205** was transformed into the final product **206** in eight steps, nucleophilic addition of a geranyl tin reagent being one of the key steps. The other key step was a selective monochlorination. The possibility of ring opening of the pyranone ring in **204** during annulation is evidently ruled out on the basis of an unfavorable stereoelectronic effect in the initial Michael adduct.

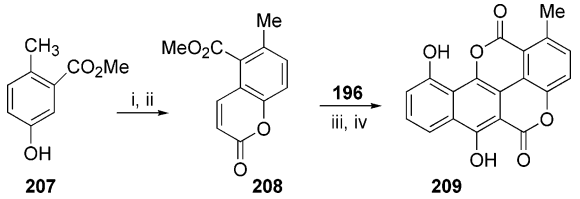
Mal et al.[15] formulated a double-annulation route based upon use of the Hauser annulation on coumarins. In-situ trapping of the aryloxy anion of the Hauser product by a proximate ester group (Scheme 43) resulting in annulation of two rings in one pot led to a concise synthesis of highly condensed and functionalized chartarin (**209**), aglycon of chartreusin. The coumarin **208** obtained in two steps from **207** was reacted with 4-methoxy-3-cyanophthalide (**196**) to give double-annulated product in 86% yield, which on HBr-promoted dealkylation produced chartarin (**209**).

Scheme 42. Total Synthesis of Napyradiomycin A1[a]



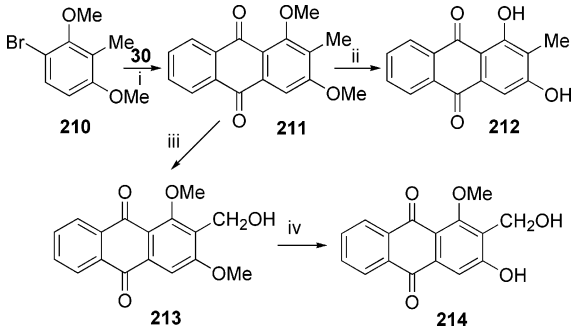
[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) MnO_2; overall 64% for two steps.

Scheme 43. Total Synthesis of Chartarin[a]



[a] Reagents and conditions: (i) $(CH_2)_6N_4$, PPA, 100 °C; 30%. (ii) $Ph_3P{=}CHCO_2Et$, Et_2NPh, reflux; 95%. (iii) LTB, THF, −60 °C; 86%. (iv) HBr, AcOH, reflux; 81%.

Scheme 44. Synthesis of Rubiadin and Damnacathol[a]



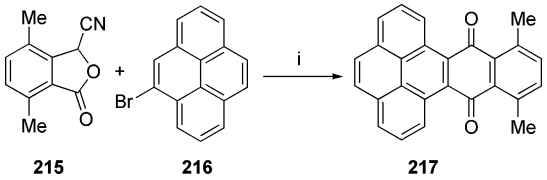
[a] Reagents and conditions: (i) LDA, THF, −78 °C, 50%. (ii) BBr_3; 61%. (iii) CAN, AcOH; 64%. (iv) 48% HBr, AcOH; 60%.

4.4. Arynes

Annulation by interception of arynes by a phthalide anion was first discovered in 1981 by Dodsworth et al.[77] In the same year, Russell and Warrener[78] observed that the annulation is possible with Hauser donors, and anthraquinones can readily and regioselectively be synthesized by a route bypassing the aerial oxidation step required by the Dodsworth route. Khanapure et al.[29a] advanced the strategy to the synthesis of various naturally occurring anthraquinones and more recently to rubiadin (**212**) and damnacathol (**214**) (Scheme 44). The anthraquinone **211** prepared from **210** served as the common intermediate for the synthesis of natural products **212** and **214**.[79]

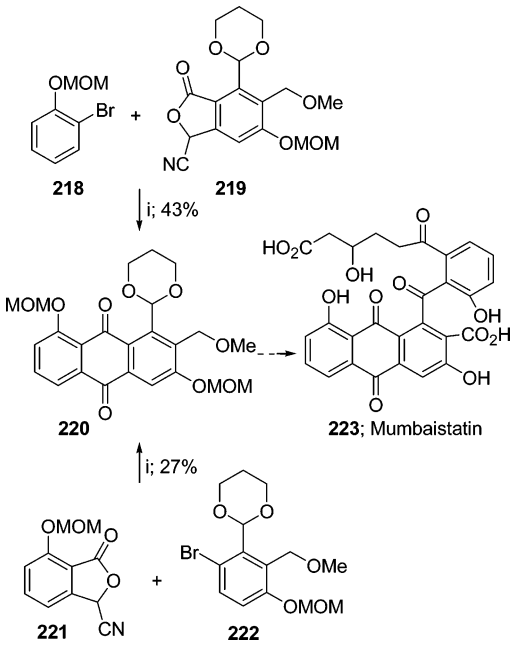
Pyrynes could also be used as acceptors for an entry to the hexanuclear quinones. Thus, reaction of **216** with cyanophthalide **215** in the presence of LDA gave dibenzo-[*de*,*qr*]naphthacene-9,14-dione **217**. The *peri*-methyl groups

Scheme 45[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C; 54%.

Scheme 46[a]



[a] Reagents and conditions: (i) LiTMP, THF, −78 °C.

present in the donor do not seem to have any effect on the yield of the reaction (Scheme 45).[80]

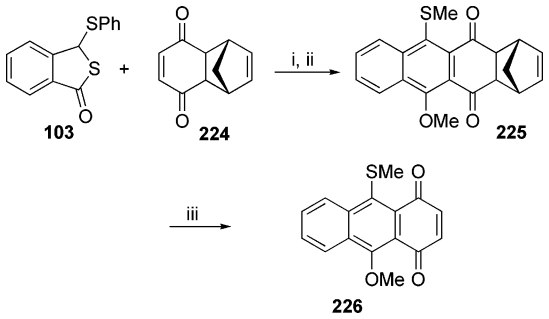
With this aryne methodology, Kaiser et al.[81] could achieve a regioselective synthesis of oxygenated anthracene-1-carboxaldehyde **220** by two complementary routes (Scheme 46) in their synthetic study of mumbaistatin (**223**). The two routes differ in the transposition of donor−acceptor properties of the annulating agents. This study resulted in improved yields of the product **220**.

4.5. *p*-Quinones

Although *p*-quinones are well known to undergo nucleophilic reactions, they were reported not to undergo Hauser annulations to give the corresponding dihydroxyanthraquinones.[78] Consequently, use of masked benzoquinone **224** was reported for an improved synthesis of 1,4-anthraquinones as illustrated by the annulation of 3-phenylsulfanylthiophthalide **103** with tricyclic enedione **224** to give the pentacyclic naphthacenedione **225** after methylation with dimethyl sulfate. Pyrolytic decomposition of the adduct **225** furnished the 1,4-anthraquinone **226** in excellent yield (Scheme 47).[82] This method has been found to be quite general for various Hauser donors such as dimethoxy-substituted phthalide sulfones **139**.

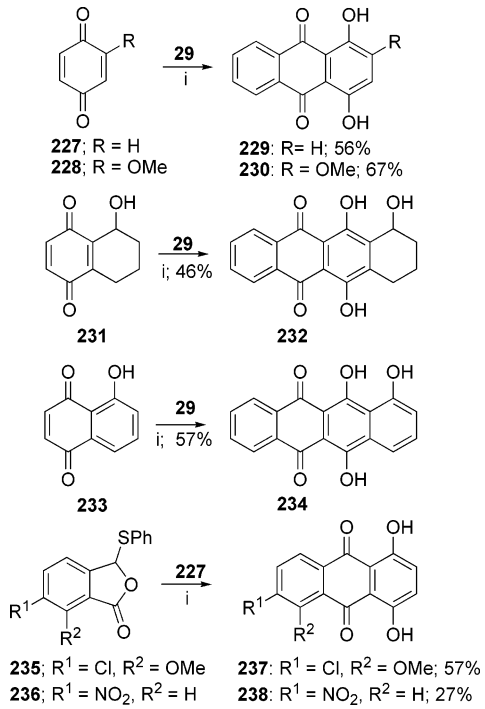
In a very recent study, Mal et al.[32] demonstrated that *p*-benzoquinones and naphthoquinones undergo Hauser annulation under select reaction conditions. As exemplified in Scheme 48, a variety of 1,4-dihydroxyanthraquinones can be prepared in a single step. The reactions are general though very much sensitive toward the nature of bases and phthal-

Scheme 47[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C. (ii) Me_2SO_4, K_2CO_3, acetone; overall 78% for two steps. (iii) FVP; >90%.

Scheme 48[a]



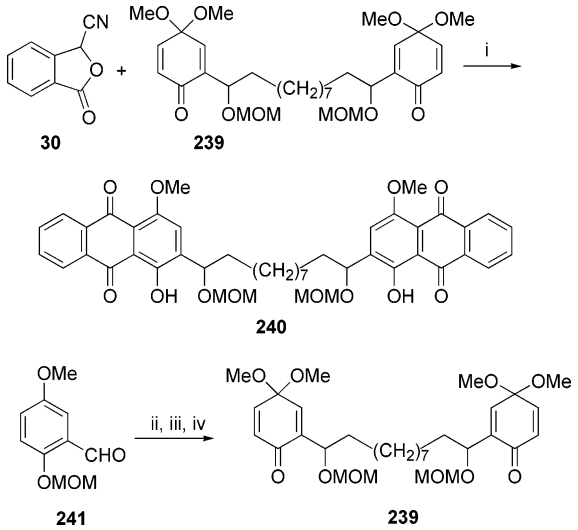
[a] Reagents and conditions: (i) LTB, THF, −60 °C.

ides. Best results are obtained with a combination of 3-phenylsulfanylphthalides (e.g., **29**) and LTB. A free phenolic OH group does not impede the annulation so as a free alcoholic OH group.

4.6. *p*-Quinone Monoketals

Quinone monoketals are considered to be the poorest class of Michael acceptors though they possess a C−C double bond conjugated to the carbonyl group of a cyclohexane ring. Only under special reaction conditions and with special reagents they undergo Michael addition with a carbon nucleophile.[83] In contrast, their reactivity matches well with the Hauser anions for formation of hydroxyanthraquinones in a single step.[84] All steps occur under basic conditions but at different temperatures. The major byproducts are the initial Michael adducts. Quinone ketals have been very popular acceptors in the Hauser reaction for the regiocontrolled target synthesis of quinonoids. The synthetic utility of the Hauser annulation was primarily and extensively established by the study on quinone monoketals that serve as building blocks in the construction of anthracyclines and angucyclines. Much of the subtopic has been highlighted in the first review.[13]

Scheme 49[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C; 70%. (ii) Mg, THF, $BrCH_2(CH_2)_7CH_2Br$. (iii) MOMCl, *i*-Pr_2NEt. (iv) [E+]/CH_3OH, $LiClO_4$, NaOAc.

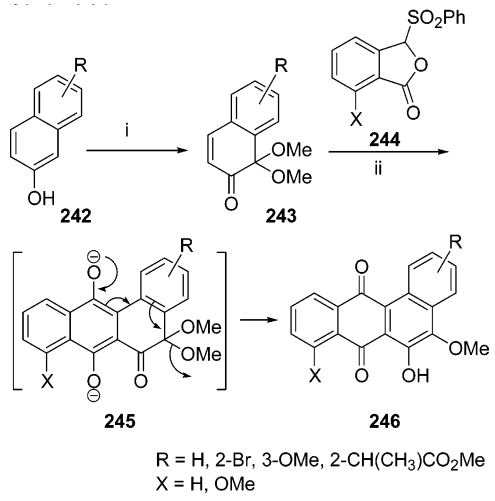
Ge and Russell[85] recently showed that two annulations are possible in one pot if an acceptor has two quinone monoketal units and synthesized DNA bisintercalators (e.g., **240**) by annulation of an alkane spacer linked *p*-quinone bismonoketal (e.g., **239**) with cyanophthalide **30** in a yield of 60−67% (Scheme 49). The annulation was not sensitive to the chain length of the spacer.

4.7. *o*-Quinone Monoketals

Compared to *p*-quinone monoketals, use of *o*-quinone monoketals has been more recent. This is partly because of the fact that many of them are not amenable to purification and their shelf life is short for the organic synthesis. However, Mitchell and Russell[86] have shown that they are sufficiently stable under basic conditions and can be engaged in annulations with Hauser donors to give 1,2-dioxygenated anthraquinones in good yields. If the monoketals are prepared from the corresponding phenol by their reaction with hypervalent iodine reagents, they need not be isolated before use in the annulation reactions. In the same year, Mal et al.[87] reported Hauser annulation of *o*-naphthoquinone monoketals (e.g., **243**) and showed that their reaction with Hauser donors in the presence of LTB smoothly takes place, resulting in rapid preparations of 5,6-dioxygenated benz[*a*]anthraquinones embedded in angucyclines (Scheme 50). The Hauser annulation cascade does not stop at the quinol corresponding to the dioxide **245** when a strong acid, such as HCl, is used during workup. It further progresses to give the anthraquinone core **246** through expulsion of a methoxy group from the intermediate hydroquinone. Hauser et al.[88] have shown that the elimination can be arrested using a weak acid, e.g., acetic acid, during workup of the reaction, and the expected quinol form **245** can be exclusively isolated as the only product.

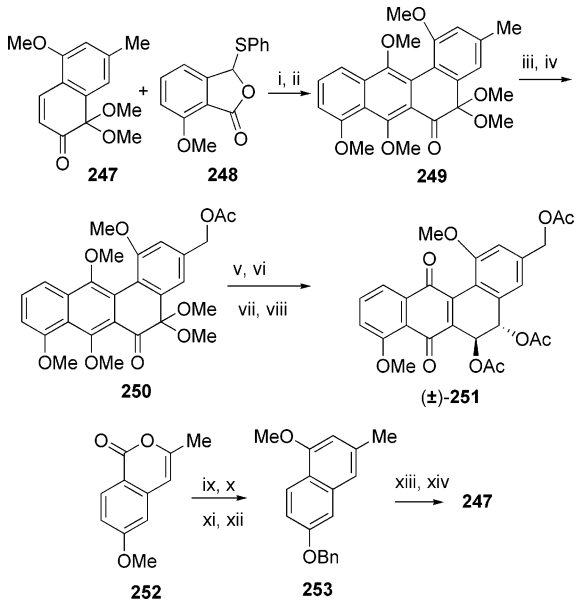
Hauser et al.[88] exploited the reaction in the total synthesis of angucyclines. They were able to intercept the reactions at the hydroquinone stage and protected it as its dimethyl ether form (e.g., **249**). Finally, they accomplished the first total synthesis of **251**, a racemic derivative of PD 116740, one of the two angucyclines with 5,6-dihydroxy groups (Scheme 51). This synthesis of Hauser et al. additionally showed that synthesis of a naphthalene derivative could be

Scheme 50[a]



[a] Reagents and conditions: (i) PIDA, MeOH; 43−88%. (ii) LTB, THF, −60 °C; 55−98%.

Scheme 51. Synthesis of PD116740 Derivative[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C; 72%. (ii) Me_2SO_4, K_2CO_3; 91%. (iii) NBS, *hν*; 48%. (iv) NaOAc, DMF; 87%. (v) TFA; 98%. (vi) $NaBH_4$, EtOH; 48%. (vii) Ac_2O, Py; 90%. (viii) CAN; 74%. (ix) BBr_3, DCM. (x) BnBr, K_2CO_3. (xi) $CH_3P(O)(OMe)_2$, *n*-BuLi, −78 °C to rt. (xii) Me_2SO_4, K_2CO_3; 75% in four steps. (xiii) H_2, Pd/C; 96%. (xiv) PIDA, MeOH; 70%.

cumbersome. The *o*-naphthoquinone monoketal **247** required for the total synthesis was prepared in a lengthy linear sequence of 11 steps from 3,4-dimethylanisole.

Annulation of quinone monoketal **247** with phenylsulfanylphthalide **248** followed by *O*-methylation with dimethyl sulfate provided methyl ether **249**. Bromination of **249** with NBS followed by treatment with NaOAc in DMF led to formation of acetoxymethyl derivative **250** in 87% yield. Sequential treatment of **250** with TFA, $NaBH_4$, Ac_2O, and CAN provided **251**. It is worth noting that in this case 3-phenylsulfanylphthalide **248** is better than the more commonly used 3-phenylsulfonyl derivative **31**, which failed to react with the monoketal **247**. Another important observation made during the investigation is that the workup procedure is crucial for trapping the desired product. When the reaction is quenched using HCl, it gives benz[*a*]anthracene-7,12-dione **254** (Figure 4), as reported by Mal et al.[87]

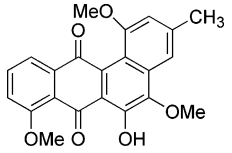
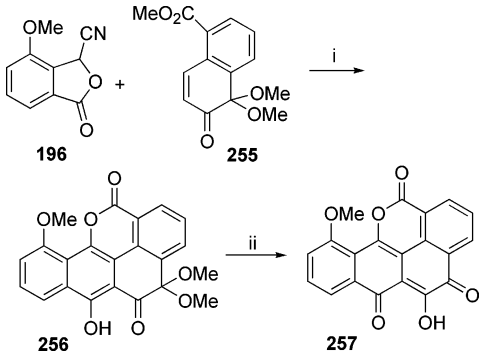


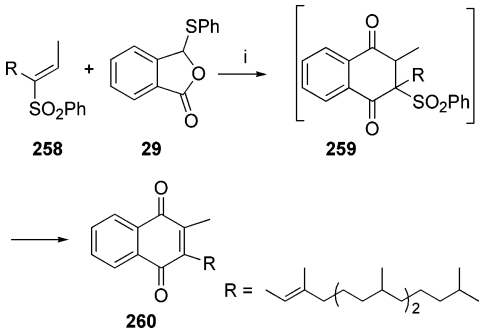
Figure 4.

Scheme 52[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C; 87%. (ii) HCl (aq,), MeOH; 98%.

Scheme 53[a]



[a] Reagents and conditions: (i) NaHMDS, THF, −78 to 10 °C; 60%.

With *o*-quinone monoketal **255** containing a proximate ester group, the Hauser annulation provided the pentacyclic skeleton **257** of the chrymutasins via formation of two rings, the second one being the pyranone ring as in **256** (Scheme 52).[15]

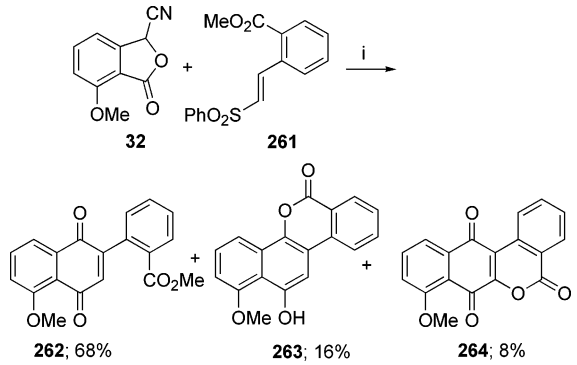
4.8. Alkenylsulfones

The first successful application of the Hauser annulation to an unsaturated sulfone was due to Tso and Chen.[89] They carried out the reaction of phthalide sulfide **29** with α,β-unsaturated sulfones (e.g., **258**) in the presence of LTB. Unlike normal cases, the products (e.g., **260**) were sulfone-free naphthoquinones (Scheme 53). The sulfone group was expelled after the initial annulation under the reaction conditions. Sulfonylphthalide **1** was less effective in the reaction. This study was extendable to the synthesis of difficult-to-obtain K vitamins[90] in moderate to good yields. The reactions were performed using NaHMDS as base.

Similar reactions with styryl sulfone **261**, as shown by Patra et al.,[91] were not clean. With **32** and **261** as reactants, three different annulation products **262**, **263**, and **264** were obtained in compliance with the initial Hauser annulation, and all of them were free from the phenylsulfonyl group (Scheme 54).

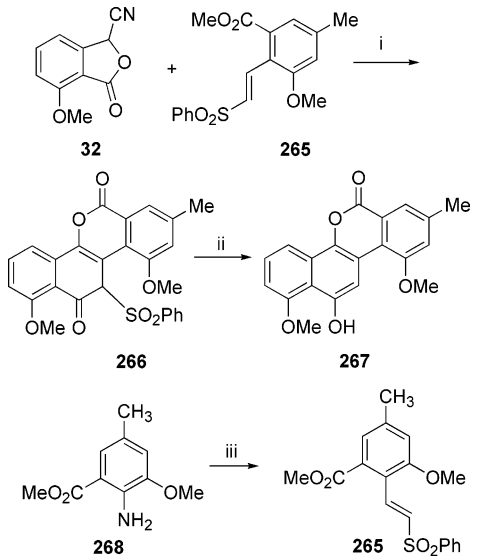
In striking contrast, more congested styryl sulfone **265** provided only one product **266**, which on desulfonylation

Scheme 54[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C; 93−98%.

Scheme 55[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C; 93−98%. (ii) Bu_3SnCl, $NaBH_3CN$, *n*-BuOH; 94%. (iii) HBF_4, $NaNO_2$, H_2O, $CH_2{=}CHSO_2Ph$, $Pd(OAc)_2$; 88%.

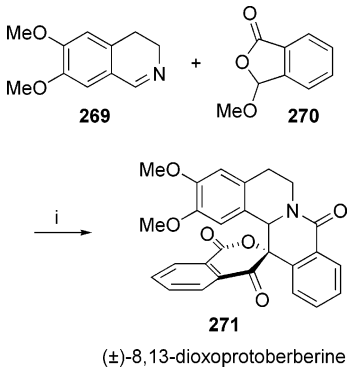
with Bu_3SnCl and sodium cyanoborohydride gave the tetracyclic skeleton of gilvocarcin **267**. The acceptor sulfone **265** was conveniently prepared by Heck reaction of diazonium salt of **268** with phenyl vinylsulfone (Scheme 55).[91]

4.9. Miscellaneous Acceptors

Although it was established that the anions of 3-unsubstituted phthalides undergo annulation with 3,4-dihydroisoquinolines to give 13-hydroxyprotoberberine alkaloids,[92] similar reactions with the anions of 3-cyano- and 3-phenylsulfonylphthalide were not successful.[42] On the contrary, the anion of 3-methoxyphthalide **270**, prepared by deprotonation with LDA, furnished double-annulated spirocyclic compound **271** in 51% yield in reaction with **269** (Scheme 56).

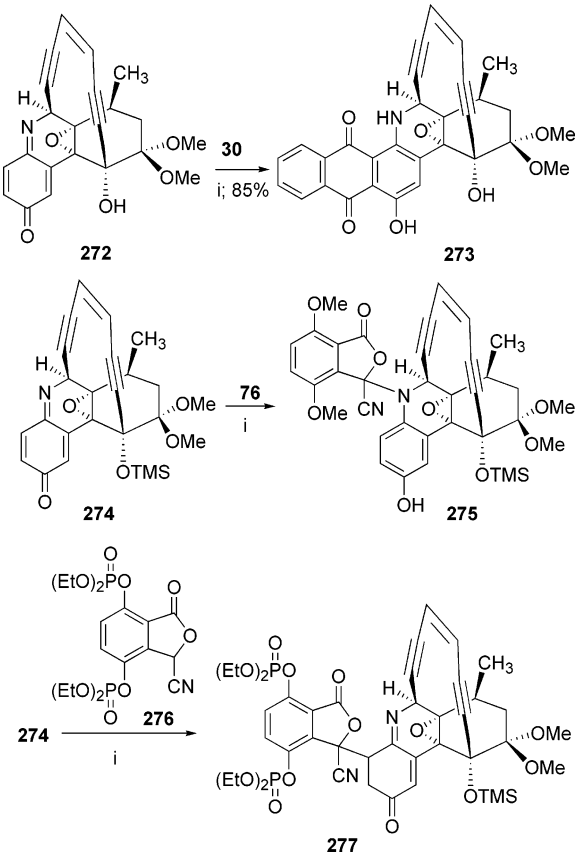
Annulation of a quinone imine with the anion of a cyanophthalide to produce aminoanthraquinone was first reported by Swenton et al.[93] In the area of total synthesis of dynemicins, Swenton's result was extended to the more complex imine by the Myers group and the Danishefsky group with mixed success. Through rigorous experimentations it was possible to assemble the multicyclic skeleton of dynemicin as shown in the late stages of the total synthesis, exemplifying the versatility of the Hauser annulation. Myers et al.[94] used quinone imine **272** as Hauser acceptor in their

Scheme 56[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C, inverse addition; 51%.

Scheme 57[a]



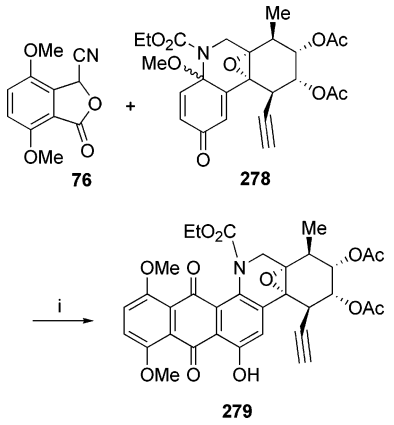
[a] Reagents and conditions: (i) LDA, THF, −78 °C.

synthesis of dideoxydynemicin. The reaction proceeded in 85% yield when unsubstituted cyanophthalide was used as Hauser donor. However, the similar annulation with 4,7-dimethoxy cyanophthalide **76** or cyanophthalide-4,7-bisphosphonate **276** failed to give the dynemicin skeleton. Instead, addition products **275** and **277** were obtained, respectively (Scheme 57).

Under the conditions of Yoon et al.[95] the same cyanophthalide, i.e., **76**, reacted with aminal **278** to give hexacyclic intermediate **279** (Scheme 58). However, a quinone aminal bearing a cyclic enediyne moiety did not respond to the Hauser annulation with **76**.

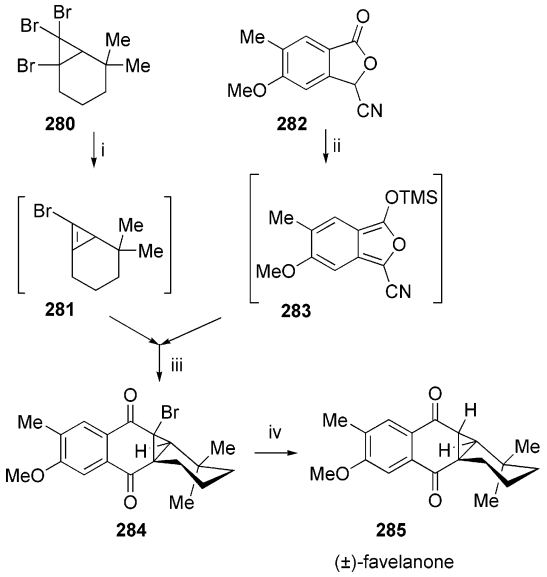
With highly activated alkenes such as bicyclo[4.1.0]-heptenes, the Hauser annulation proceeds smoothly to give cyclopropanaphthoquinones. Such a reaction proved useful in the total synthesis of naturally occurring tetracyclic

Scheme 58[a]



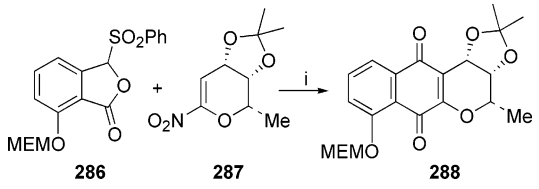
[a] Reagents and conditions: (i) LTB, THF, 0 °C to reflux; 37%.

Scheme 59. Synthesis of Favelanone[a]



[a] Reagents and conditions: (i) *n*-BuLi, THF, −100 °C. (ii) LDA, THF, −78 °C, TMSCl. (iii) rt then H_3O^+. (iv) Bu_3SnH, AIBN; overall 15% yield.

Scheme 60[a]



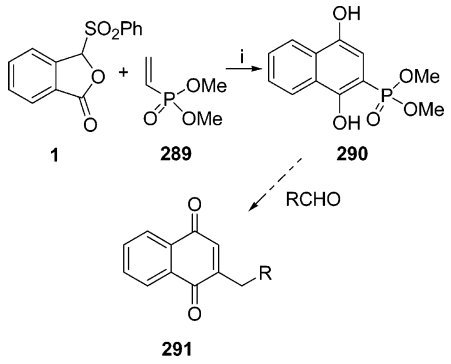
[a] Reagents and conditions: (i) LDA, THF, −78 °C; 65%.

favelanone (**285**). The reactive intermediates **281** and **283**, without isolation, were allowed to react together to produce **284**. Debromination of **284** by Bu_3SnH afforded favelanone (**285**) in an overall yield of 15% (Scheme 59).[96]

Nitroalkenes are well-known Michael acceptors. Except for two reports,[97] they have not received much attention in the context of the Hauser annulation. The work of Brade and Vasella[97b] on naphtho[2,3-*b*]pyrandiones is noteworthy. Reaction of phthalide sulfone **286** with nitroglycal **287** directly gave the naphthoquinone **288** (65% yield) (Scheme 60), deprotection of which gave the enantiomer of (−)-cryptosporin. Under the reaction conditions, the nitro group of the initial annulated product was eliminated.

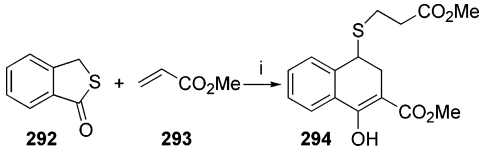
In an attempt to develop a new synthesis of 2-alkylnaphthoquinone, vinylphosphonate **289** was reacted with sulfonylphthalide **1** to give hydroquinone **290**, further elaboration of which via Wittig−Horner reaction under a variety of conditions remained unsuccessful (Scheme 61).[98]

Scheme 61[a]



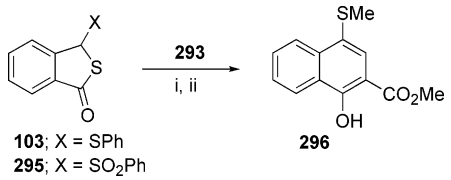
[a] Reagents and conditions: (i) LTB, THF, −60 °C.

Scheme 62[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C; 26%.

Scheme 63[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C. (ii) MeI; >90%.

5. Analogs of Hauser Donors

5.1. Thiophthalide Analog

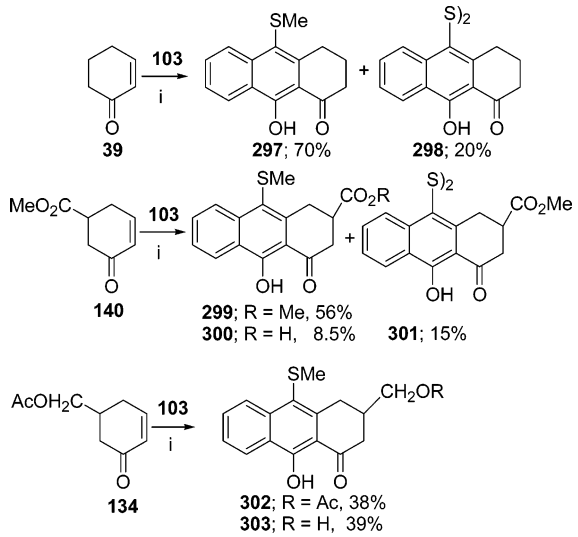
The need for structural modification of Hauser's isobenzofuranones in favor of thiophthalides (e.g., **292**) stemmed from assembling of the hydroaromatic part of natural products like olivin and pillaromycin. Although thiophthalides (**292**) could be lithiated like phthalides (e.g., **33**), the resulting anions appeared to be less stable than those derived from phthalides (e.g., **33**). Attempted cyclocondensation of **292** with methyl acrylate (**293**) in the presence of LDA afforded an intractable mixture of products. Switching to LTB from LDA in a similar reaction resulted in formation of the annulated product **294** in 26% yield (Scheme 62).[99] The trend of low to moderate yields of annulation was also observed with other substituted thiophthalides as well as acceptors.

When the C-3 substituted derivatives of **292**, i.e., **103** and 2**95**, were investigated, the efficiency of the annulations increased enormously, possibly due to a substantial increase in the acidity of the C-3 hydrogen (Scheme 63). Reaction of **103** has been generalized with several examples. In all cases studied, yields of the products were very high (Scheme 64).[100]

5.2. Isoxazole Analog

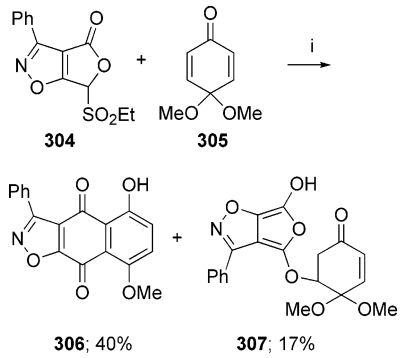
While extension of the Hauser reaction to the heterocyclic analogs of isobenzofuranones is obviously conceivable, it

Scheme 64. Annulation of 3-(Phenylthio)thiophthalide 86 with Cyclohexenones[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C then MeI at rt.

Scheme 65[a]



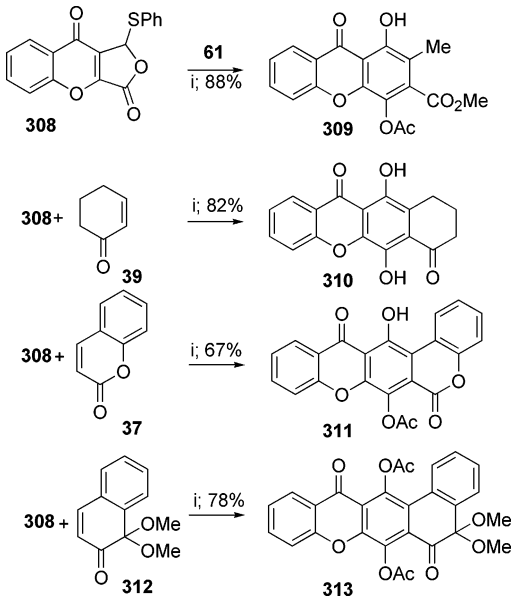
[a] Reagents and conditions: (i) LHMDS, −78 °C.

was not reported until 1995 by Alguacil et al.[101] In pursuit of generating heterocyclic analogues of anthracyclines, they investigated the reactivity of isoxazole-fused furanone **304** with functionalized quinone monoketals, and the corresponding annulated products could be prepared in moderate yields. The reaction of isoxazole sulfone **304** with benzoquinone monoketal (**305**) in the presence of LHMDS afforded after 15 days at −15 °C a mixture of naphthoisoxazole **306** in 40% yield and compound **307** in 17% yield (Scheme 65). The atypical formation of the Michael adduct **307** is explained in terms of nucleophilic attack of the resonance-stabilized anion through the oxygen at the 4-position. The structure of **307** was confirmed by analysis of spectral data.

5.3. Benzopyranone Analog

Hauser et al.,[76] in their total synthesis of bikavarin, a xanthone natural product, explored the possibility of annulation of benzopyranone with an isobenzofuranone and were successful in accomplishing a total synthesis. However, the scheme was impeded by the low yield of the annulation step. As a remedy to this problem, Hauser and Dorsch[102] considered transposition of the reactivity of the reactants and extended their work to development of a general synthesis of xanthones using heterocyclic donors. Benzopyranofuranone **308** reacted smoothly with unsaturated carbonyl compounds to give the corresponding xanthones in high yields. It is interesting to note that the SPh group is

Scheme 66[a,b]



[a] Reagents and conditions: (i) LTB, THF, −78 °C, Ac_2O. [b] Reaction of **39** with **308** was not quenched with Ac_2O.

sufficiently activating to assist formation of incipient carbanion at its α position. Preparation and use of the corresponding $PhSO_2$ derivative was not required. The results presented in Scheme 66 illustrate the versatility of the annulation of **308** with a variety of Michael acceptors, thus providing an efficient synthesis of xanthones.

5.4. Indole Analog

Entry to the synthesis of carbazole quinones by application of a Hauser annulation was recently investigated by Mal et al.[29b,c] Annulation of 4-ethoxycarbonyl-1-phenylsulfonyl furoindolone (**314**) with *o*- and *p*-quinone monoketals provided the corresponding indoloquinones **316**, **318**, and **320** in good yields (Scheme 67). LTB was found to be better than LDA as a base. Interestingly, no separate step was required to remove the ethoxycarbonyl protecting group if the reaction mixture was stirred at room temperature before workup. In many instances, the in-situ deprotection appeared to be an impediment to the annulation. Fused cyclohexadienones with an angular methoxy group as in **43** and **321** did not react with **314**, possibly due to steric hindrance. Similarly, reaction of 2-cyclohexenone (**39**) also failed, possibly due to its base-catalyzed self-condensation.

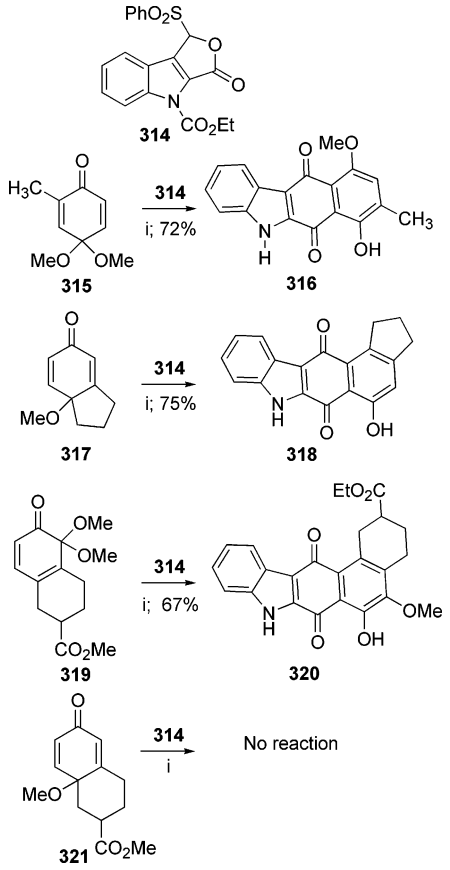
5.5. Dimeric Analog

Hauser and Gauuan[103] advanced the chemistry of the annulation to the dimeric form of sulfonylphthalides and achieved a neat synthesis of (±)-biphyscion (**324**). The lesson from this study is that two anionic annulations can be performed in a one-pot operation. Annulation of **322** with **133** followed by oxidation with $Ag_2CO_3-Et_3N$ gave **323** in 36% yield. MgI_2-assisted demethylation afforded (±)-biphyscion (**324**) (Scheme 68).

5.6. Naphthofuranone and Furanone Analogs

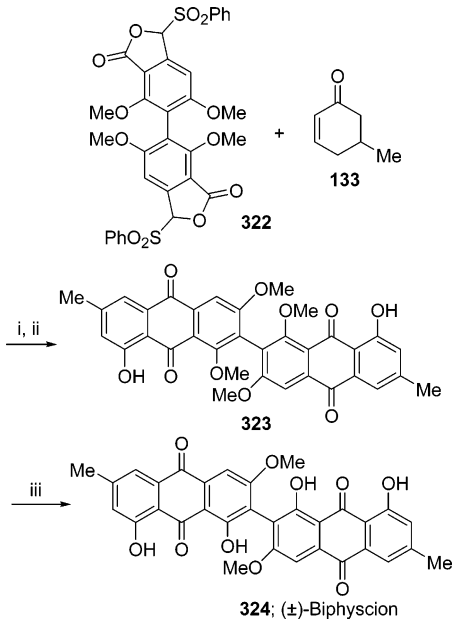
That the reactivity of naphthoisofuranone sulfones (e.g., **325**) is very similar to that of isobenzofuranone sulfones was demonstrated by Hauser and Prasanna[47a] in 1981. Apparently, the presence of an additional benzene ring in the former has

Scheme 67[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C.

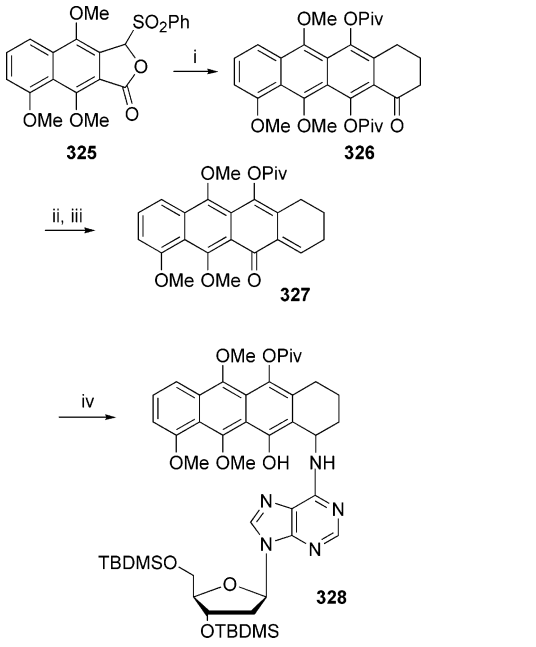
Scheme 68. Synthesis of Biphyscion[a]



[a] Reagents and conditions: (i) LTB, THF, −78 °C. (ii) Ag_2CO_3, Et_3N, CH_2Cl_2; overall 36% for two steps. (iii) $MgI_2.Et_2O$; 70%.

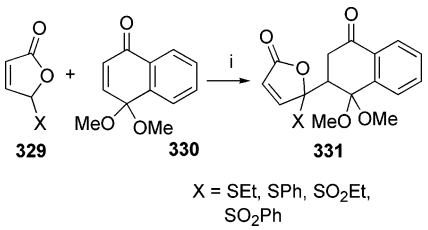
no significant effect on their annulation reaction. In an effort to further the understanding of the chemistry of anthracycline-type quinone methides, Angle et al.[104] prepared tetracyclic *o*-quinone methide **327** starting from the known sulfone **325**. Annulation of sulfone **325** with cyclohexenone (**39**) in the presence of LDA, followed by masking of the resulting hydroquinone as the bispivalate, afforded **326** in

Scheme 69[a]



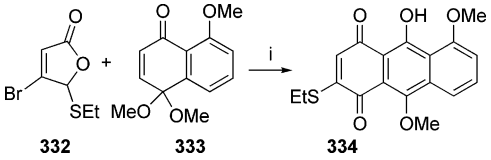
[a] Reagents and conditions: (i) LDA, 2-cyclohexenone, PivCl, DMAP; 58%. (ii) $NaBH_4$; 59%. (iii) Ag_2O. (iv) TBDMS-protected 2-deoxyadenosine; ∼33%.

Scheme 70[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C; 68−78%.

Scheme 71[a]



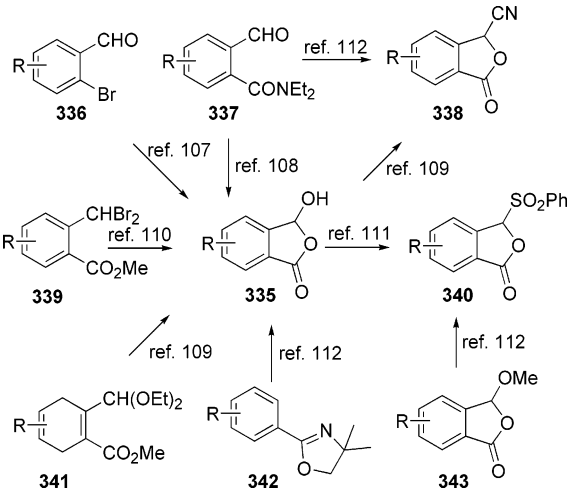
[a] Reagents and conditions: (i) LDA, THF, −78 °C; 36%.

58% yield. This adduct was converted to the quinone precursor, which was oxidized with silver oxide to give quinone methide **327**. Among many kinds of nucleophiles, *O*-silylated adenosine was reacted with **327** to give the adduct **328**, supporting Moore's bioreductive alkylation formalism[105] of biological activities of anthracyclines and related quinones (Scheme 69).

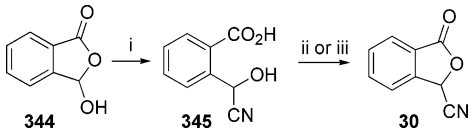
In contrast to the isobenzofuranone Hauser donors and their benzene homologs, the monocyclic furanones (e.g., **329**) are poor donors. Asenjo et al.[106] have shown that 2-furanones (**329**) substituted at the 5-position by sulfur-bearing groups such as SEt, SPh, SO_2Et, and SO_2Ph do not undergo annulation with naphthoquinone monoketals **330**. Rather, they give Michael adducts **331** in the presence of LDA (Scheme 70) in 68−78% yield.

However, the similar furanone **332** with a 4-bromo substituent furnished bromine-free annulated product **334** in 36% yield after 13 days of reaction (Scheme 71).[106]

Scheme 72. Protocols for the Synthesis of Hauser Donors

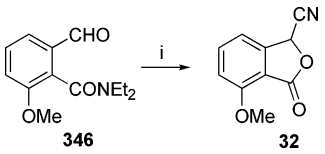


Scheme 73[a]



[a] Reagents and conditions: (i) KCN, HCl, 0 °C; 77%. (ii) $(COCl)_2$, DMF, Py, CH_3CN; 82%. (iii) DCC, rt; 82%.

Scheme 74[a]



[a] Reagents and conditions: (i) NaCN, PTSA, THF/H_2O; 95%.

6. Preparation of Isobenzofuranones

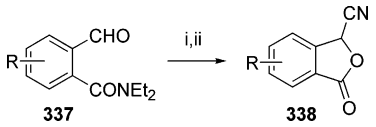
Phthalaldehydic acids **335** are useful synthons for a number of classes of natural products including phthalide isoquinolone alkaloids, some of which exhibit central nervous system activities. They are also most useful intermediates for the preparation of Hauser donors. Although a variety of ortho-substituted benzene derivatives can be transformed to phthalaldehydic acids, use of the ortho formylbenzamide derivatives **337**, obtainable via orthometalation methodologies, has been the preferred strategy (Scheme 72).

For the preparation of 3-cyanophthalides (**30**), phthalaldehydic acids (e.g., **344**) are normally submitted to the methods of Freskos et al.[109] or Russell et al.[113] (Scheme 73). Freskos et al. cyclized the cyanohydrins (e.g., **345**) using Vilsmeier salt derived from oxalyl chloride and DMF, whereas Russell et al. used DCC for the cyclization. The superiority of the Russell method has been noted in the preparation of fluoro-substituted cyanophthalides.

Li and Wu[114] reported an interesting conversion of the readily accessible formylbenzamides. 3-Cyano-7-methoxyphthalide **32** was prepared in one step in 95% yield from *N*,*N*-diethyl-2-formyl-6-methoxybenzamide (**346**) by treatment with sodium cyanide and an equivalent amount of PTSA in aqueous THF at 0 °C to room temperature (Scheme 74). However, the reaction gave variable yields of products when applied to other functionalized amides.

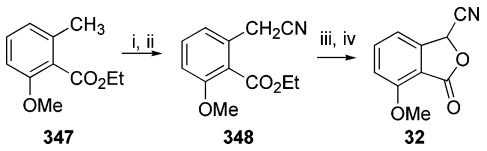
The protocol of Okazaki et al.[115] for conversion of *N*,*N*-diethyl-6-formylbenzamides **337** with different nuclear substituents to the corresponding cyanophthalides **338** involves

Scheme 75[a]



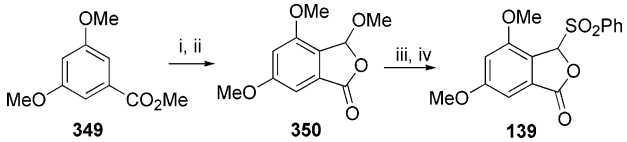
[a] Reagents and conditions: (i) TMSCN, KCN, 18-crown-6, CH_2Cl_2. (ii) CH_3COOH; >80% in two steps.

Scheme 76[a]



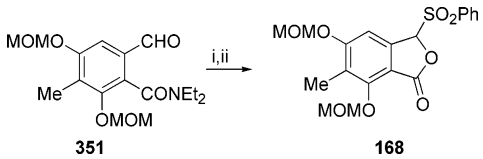
[a] Reagents and conditions: (i) NBS. (ii) NaCN; overall 83% for two steps. (iii) NBS. (iv) heat; overall 49% for two steps.

Scheme 77[a]



[a] Reagents and conditions: (i) $CHCl_2OMe$, $TiCl_4$. (ii) MeOH, H^+; 70%. (iii) PhSH, PTSA; 85%. (iv) H_2O_2, AcOH; 88%.

Scheme 78[a]



[a] Reagents and conditions: (i) $PhSO_2Na$, AcOH, 80 °C; 66%. (ii) MOMCl, *i*-Pr_2NEt, DMF; 74%.

treatment of TMSCN and KCN in the presence of 18-crown-6. This method appears to be the most general (Scheme 75).

Kraus et al.[35] adopted a thermal cyclization strategy probably initiated by neighboring-group participation. The cyanotoluate **348**, prepared from **347** by NBS bromination followed by displacement of the bromine with cyanide, was again brominated to give the corresponding benzylic bromo compound which on heating gave cyanophthalide **32** (Scheme 76).

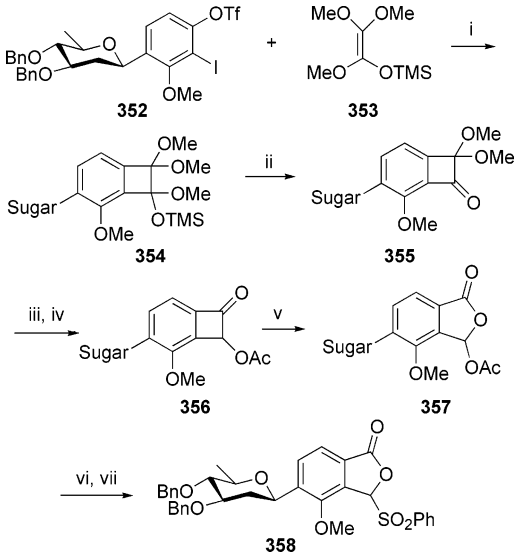
The oxazoline route was employed by Meyers and Avila[112] to synthesize the sulfonyl phthalides (**340**). A similar strategy was also utilized by Russell and Warrener[116] for the synthesis of (1-^{13}C)-labeled cyanophthalide en route to labeled anthracyclines.

Murty et al.[58] used dichloromethyl methyl ether for formylation of dimethoxybenzoate **349** and synthesized the corresponding phthalide sulfone **139** from methoxy phthalide **350** as outlined in Scheme 77.

Tatsuta et al.[65] showed that the furanone ring of an isobenzofuranone, e.g., **168**, can be directly built up from ortho-formylated benzamide **351** by reacting with sodium benzenesulfinate at 80 °C in acetic acid medium (Scheme 78). A similar principle was used for phenolic phthalide sulfone.

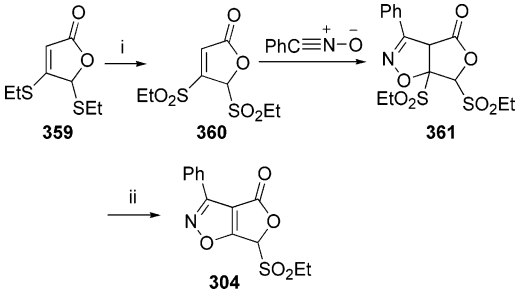
Synthesis of Suzuki's phthalide sulfone **358** containing a *β*-*C*-olivoside unit is entirely different from those discussed above. It does not involve commonly used phthalaldehydic acid precursors but benzocyclobutane derivatives. The sequence features a regioselective [2 + 2] cycloaddition of benzyne with ketene silyl acetal and an unusual Baeyer−

Scheme 79[a]



[a] Reagents and conditions: (i) *n*-BuLi. (ii) KF, $(n\text{-Bu})_4NCl$; 73% for two steps. (iii) $NaBH_4$, MeOH, THF, O °C, 15 min; then 4 M HCl (aq) 2 h; 98%. (iv) Ac_2O; 93%. (v) MCPBA; 95%. (vi) PhSH, PTSA; 97%. (vii) MCPBA; 95%.

Scheme 80[a]



[a] Reagents and conditions: (i) MCPBA (2 equiv). (ii) silica gel; >65%.

Villiger reaction. Thus, the mixture of triflate **352** and acetal **353** when treated with *n*-BuLi gave **354** as a single product. Subsequent hydrolysis and $NaBH_4$ reduction generated **356**. Regioselective Baeyer−Villiger oxidation with MCPBA resulted in **357**. Two more steps, i.e., thioether formation and MCPBA oxidation, led to the preparation of the needed phthalide sulfone **358** (Scheme 79).[117] It is noteworthy that application of a similar sequence to a monomethoxy ketene acetal led to the synthesis of an isomer of phthalide sulfone **358**.[118]

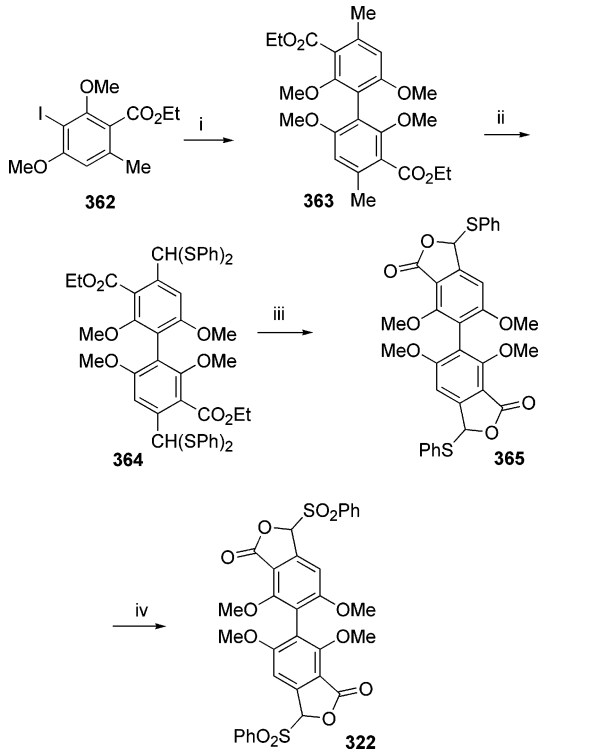
Intermolecular nitrile oxide cycloaddition to furanone **360** was the key step for the synthesis of isooxazoloisobenzofuranone **361**. Loss of the resulting angular sulfone group gave Hauser donor **304** (Scheme 80).[101a]

Hauser bis-isobenzofuranone synthesis was based upon the lateral phenylsulfenation of an ortho toluate **362**, earlier developed by his group. Sulfenation of **363** gave **364**, which was cyclized to isobenzofuranone **365** by TFA treatment. MCPBA oxidation furnished bis(sulfonylisobenzofuranone) **322** in 100% yield (Scheme 81).[103]

Functionalization of thiophthalide **292** at the 3-position to form a Hauser donor has been performed via benzylic bromination or lateral sulfenation. Barring the sulfenation step, all steps depicted in Scheme 82 are high yielding.[100]

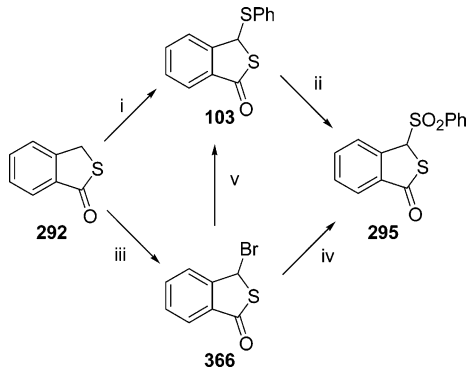
Synthesis of the benzopyranone Hauser donor **308** features a Pummerer rearrangement. The known benzopyranone **367**, obtained from *o*-hydroxypropiophenone and ethyl chloroxoacetate, was elaborated in five steps to benzopyranofuranone **308**, the key step being an intramolecular Pummerer cyclization of sulfoxide **369** (Scheme 83).[37]

Scheme 81[a]



[a] Reagents and conditions: (i) Cu-bronze, 210−220 °C; 72%. (ii) LDA, $(PhS)_2$, −78 °C; 55%. (iii) TFA, H_2O, heat; 100%. (iv) MCPBA, K_2CO_3; 100%.

Scheme 82[a]



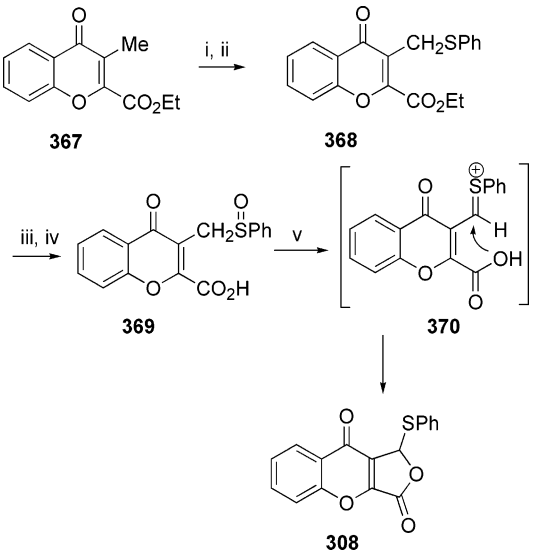
[a] Reagents and conditions: (i) LDA, PhSSPh or $PhSSO_2Ph$; 30%. (ii) H_2O_2 (30%), AcOH, 50 °C; 90%. (iii) NBS, CCl_4, light; 99%. (iv) $PhSO_2Na$, DMF; 50%. (v) PhSH, Et_3N; 90%.

Usually phthalide-3-phosphonates are prepared by reaction of 3-hydroxyphthalides **335** with sodium dimethyl phosphonates in methanol.[119] In an improved version, Watanabe and Furukawa[120] utilized phthalaldehydic amides (**337**), readily accessible from the corresponding benzamides through *ortho*-lithiation followed by formylation with DMF. Phthalaldehydic amides (**337**) on reaction with *tert*-butyldimethylsilyl dimethyl phosphite followed by desilylation and cyclization using methanesulfonic acid at room temperature provided phthalide-3-phosphonates (**371**) in 71−99% yield (Scheme 84).

7. Reaction Conditions

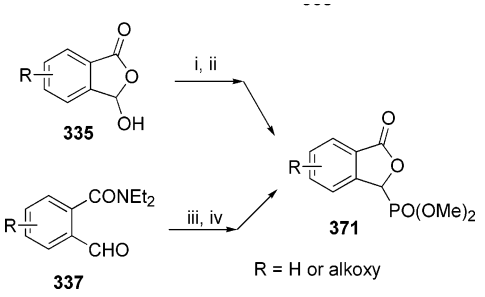
Success of the Hauser annulation crucially depends on the reactivity of reactants. The reaction is also very sensitive to

Scheme 83[a]



[a] Reagents and conditions: (i) NBS, CCl_4, *hν*; 84%. (ii) PhSH, KOH, EtOH; 97%. (iii) KOH, MeOH, H_2O. (iv) MCPBA, CH_2Cl_2. (v) Ac_2O, heat; overall 60% for three steps.

Scheme 84. Synthesis of Dimethyl Phthalide-3-phosphonate[a]



[a] Reagents and conditions: (i) $Na^+OP^-(OMe)_2$, MeOH. (ii) CH_3SO_3H. (iii) $(MeO)_2POSiMe_2(^tBu)$, benzene, rt, 12 h. (iv) CH_3SO_3H, MeOH, rt, 12 h; overall 71−99% for two steps.

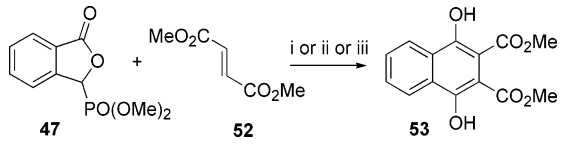
reaction conditions, barring the nature of the substituents at the 3-position. In initial publications the ratio of the Hauser donor to base was 1:2.[121] Later, it was found that a ratio of 1:3 is better for higher yields.[64a] Three-fold excess of the base could be justified on the grounds of driving the reaction to completion, giving three anions: two phenoxides and one leaving group. As the reaction progresses, the base is consumed to form the phenoxide salt.

The choice of bases was somewhat random, arbitrary, and without logistics. However, use of LTB, first reported by Hauser and Mal[64a] in 1983, is more popular than commonly used bases like KTB and LDA because of higher yields with the former. A similar observation was noted in the annulation with 3-methoxycarbonylphthalide **48**.[39] It is also true with phosphonate donor **47**. Among the three bases LTB, LDA, and NaH examined, the first one was most effective (Scheme 85).[38]

The range of reaction conditions in terms of a combination of base, solvent, additive, and temperature is wide. The reported combinations are (i) LDA−THF,[10] (ii) LDA−HMPA,[35] (iii) LDA−TMSCl,[50] (iv) LDA−$ZnCl_2$,[56] (v) MeLi−DMSO, THF,[22] (vi) LTB, [64a] (vii) LTB−LiCl,[95] (viii) KTB,[122] (ix) LiHMDS,[89] (x) NaHMDS,[89] (xi) KHMDS,[89] (xii) NaH,[38] (xiii) *sec*-BuLi,[23] and (xiv) *t*-BuLi.[30]

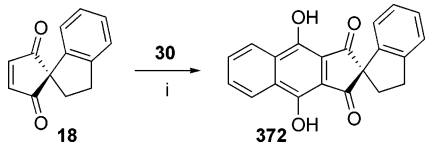
Bach et al.[30] reported that *t*-BuLi can deprotonate a phthalide (e.g., **30**) at a much faster rate than its nucleophilic

Scheme 85[a]



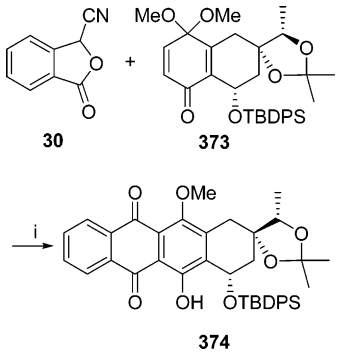
[a] Reagents and conditions: (i) LTB, THF, −78 °C to reflux, 1 h; 98%. (ii) LDA, THF, −78 °C to reflux, 1 h; 72%. (iii) NaH, THF, 0 °C to reflux, 1 h; 65%.

Scheme 86[a]



[a] Reagents and conditions: (i) *t*-BuLi; 80%.

Scheme 87[a]



[a] Reagents and conditions: (i) KTB, THF, −15 °C; 98%.

addition to the lactone carbonyl group of **30** and thus the Hauser annulation as in Scheme 86.

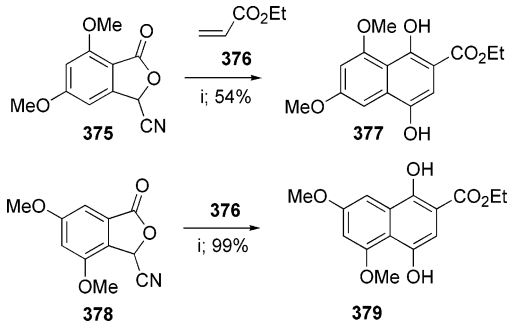
Though in most cases LTB is used as a base in the annulation reaction, Achmatowicz and Szechner[122] in their recent synthesis of idarubicinone precursor **374** used KTB at −15 °C for condensation between cyanophthalide **30** and the quinone monoketal **373**. The yield of the product was excellent, and the stereochemical integrity of the product in the chiral segment of the enone was not lost (Scheme 87).

In one instance, the sequence of addition of the reactants has been found to affect the yield of annulation.[42] The temperature of the reaction is also an important factor. When the reaction is carried out at low temperature and subsequently quenched at low temperature, Michael addition products are obtained.[50] Tso and Chen[89] observed that there is no definitive role of the effect of counterion of the bases used. The routine reaction time is about 12 h or 1 day. However, annulation of naphthoquinone monoketals with the isoxazole analog of phthalide **304** unusually takes 5 days in the presence of LDA. In one case, it took 13 days.[101b]

8. Scope and Limitations

The reaction as discussed before is very general with regard to the substrates, i.e., donors and the corresponding acceptors. It encompasses a wide variety of substrates. Remarkably, many functional groups, otherwise sensitive to strong bases like LDA and LTB, survive under the reaction conditions of the Hauser annulations. They are terminal alkynes, esters, lactones, lactams, ketones, aldehydes, nitriles, and epoxides. One possible reason for the mildness of the reactions is the low reaction temperature, i.e., −78 °C, at

Scheme 88[a]



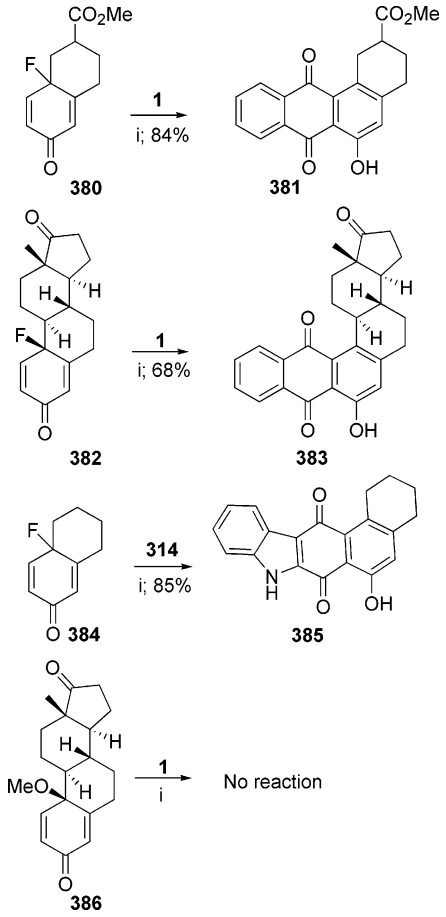
[a] Reagents and conditions: (i) *sec*-BuLi, THF, −78 °C.

which it is usually run. At this temperature, other possible side reactions are minimized. Consequently, the range of annulation products is also very broad and has been useful in the total synthesis of many kinds of natural products like anthracyclines, angucyclines, naphthopyranone antibiotics, xanthones, carbazole alkaloids, fredericamycin, granaticin, and kinamycins. Nevertheless, the reaction is not free from shortcomings.

There is little difference in reactivity between the phenylsulfonyl phthalides and the cyanophthalides, the former being easier to prepare. With cyanophthalides and Hauser acceptors having unprotected acetyl groups, formation of cyanohydrin containing annulated products is occasionally encountered.[123] Rho et al.[39] showed that in some instances the methoxy groups in the benzene ring of the Hauser donor have no marked influence on their reactivity. Similarly, the tolyl sulfone in place of phenyl sulfone does not make any difference in the net outcome.[45] Murty et al.,[58] in their quest to the unnatural anthraquinones, showed that two methoxy groups in the 1,3-positions of an isobenzofuranone led to a lower amount (15% with 5-acetoxymethylcyclohenone) of products. Very recently, Brimble et al.[23] thoroughly investigated the reactivity of two dimethoxy cyanophthalides **375** and **378**. While the cyanophthalide **378** gave a quantitative yield of the annulation product with ethyl acrylate in the presence of *sec*-BuLi, the isomeric cyanophthalide **375** gave only 54% of the annulation product under similar conditions. Quite strangely, the cyanophthalide **375**, under most commonly used conditions of the Hauser reaction, i.e., LDA (with or without HMPA), *t*-BuLi, or LTB, gave only 5% annulation product with acrylonitrile and ethyl acrylate acceptors. Use of Lewis-acid additives and inverse addition techniques did not improve the efficiency of the reaction, pointing to the dramatic effects of the nuclear methoxy substituents (Scheme 88). However, in the case of 5,7-dimethoxy-3-phenylsufonylphthlide **69**, reaction with methyl crotonate proceeded smoothly, giving compound **70** in 88% yield after methylation of the product (Scheme 10).

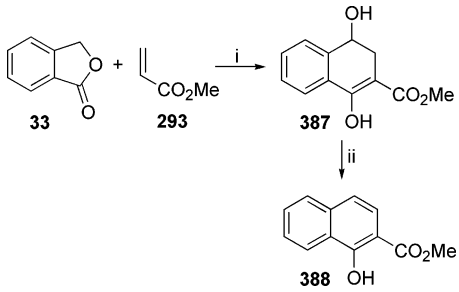
That the steric effect could be an impediment to the Hauser annulation was first noted by Mitchell and Russell[124] in their work with quinone monoketals. While 4-methoxy-4-methylcyclohex-2,5-dienone (**41**) efficiently annulates with the anion of cyanophthalide **30**, 4-*tert*-butyl-4-methoxycyclohex-2,5-dienone fails to furnish any anthraquinone product. Subsequently, the steric effect has been implicated in many instances.[15,87,88] However, only recently it has been convincingly established that the steric effect could be a major concern for the success of the annulation. The fluoro derivatives **380**, **382**, and **384** smoothly underwent annulation with Hauser donors **1** and **314** to give **381**, **383**, and **385**,

Scheme 89[a]



[a] Reagents and conditions: (i) LTB, THF, −60 °C.

Scheme 90[a]



[a] Reagents and conditions: (i) LDA, THF, −40 °C; 37%. (ii) $BF_3.Et_2O$, CH_2Cl_2, rt; 72%.

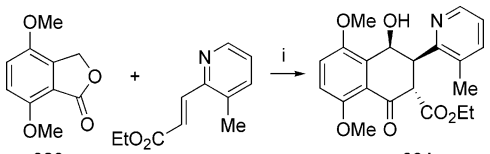
respectively. It is to be noted that the corresponding angular methoxy derivatives **43**, **321**, and **386** were completely resistant to annulation with **1** nor did they give the corresponding Michael adducts (Scheme 89).[125]

9. Allied Reactions

In 1978, Broom and Sammes[126] discovered a new synthesis of 4-hydroxytetralones and 1-naphthols based on annulation of phthalides without a C-3 substituent. As shown in Scheme 90, reaction of phthalide **33** with methyl acrylate (**293**) furnishes dihydronaphthalene derivative **387**, which upon treatment with BF_3·etherate, yields 1-hydroxynaphthalene **388**.

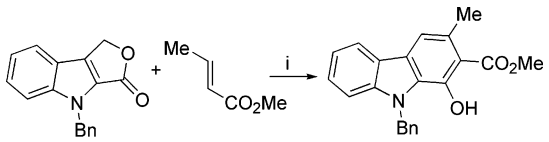
Although the reaction was general and regiospecific, the reaction did not find many applications due to its inefficiency. However, such a reaction can be very efficient in certain

Scheme 91[a]



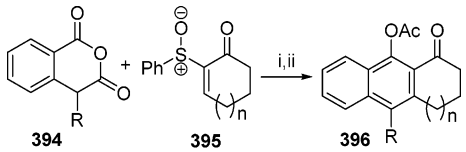
[a] Reagents and conditions: (i) LDA, THF, −78 °C; 95%.

Scheme 92[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C; 67%.

Scheme 93[a]



Compound	R	n	Yield (%)
396a	H	1	70
396b	SPh	1	58
396c	OMe	1	62
396d	H	2	60
396e	SPh	2	52

[a] Reagents and conditions: (i) NaH, 1,4-dioxane, reflux. (ii) Ac_2O, Py, rt.

cases. For instance, it has been applied to the synthesis of lignan analogs.[127]Magnus et al.,[128] in their model study to dynemicin A, showed that such a reaction could be very high yielding if a *β*-pyridylacrylate (e.g., **390**) is used as an acceptor (Scheme 91).

The indole version of the Sammes annulation has recently been realized to provide a general and one-pot synthesis of 1-hydroxycarbazoles (Scheme 92). In contrast to the original findings, the intermediacy of the tetrahydro intermediates (cf. **387**) was not observed with the indole-based donors (e.g., **392**).[129]

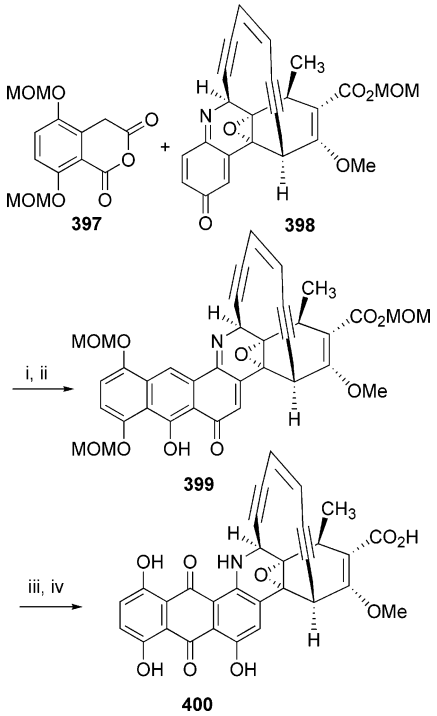
Lio et al.[130] showed that in the presence of a strong base like NaH, homophthalic anhydrides (**394**) can act as donors in annulation with enones (e.g., **395**) having a good leaving group at C-2 to give the benzannulated products (e.g., **396**) (Scheme 93).

One of the finest applications of the annulation can be found in the Danishefsky synthesis of dynemicin A (Scheme 94). The crucial annulation between **397** and **398** was sufficiently mild to accommodate acid-sensitive functional groups like epoxide, enol ether, and imines at the penultimate stage of the total synthesis.[131]

In 1978, Hauser and Rhee[10] described an annulation (Scheme 95) analogous with the titled one for the regiospecific synthesis of 1,2,3-trisubstituted naphthalenes (e.g., **402**). This reaction has generally been useful for the synthesis of natural products, such as pradimicinone analogs,[43] kidamycinone,[121] and benzo[*b*]fluorenone.[132]

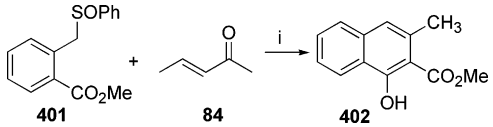
It has also been applied to the synthesis of 8-methoxypsoralen (**407**). As depicted in Scheme 96, the annulated product **404** was obtained in 73% yield from furan sulfoxide

Scheme 94. Danishefsky Synthesis of Dynemicin A[a]



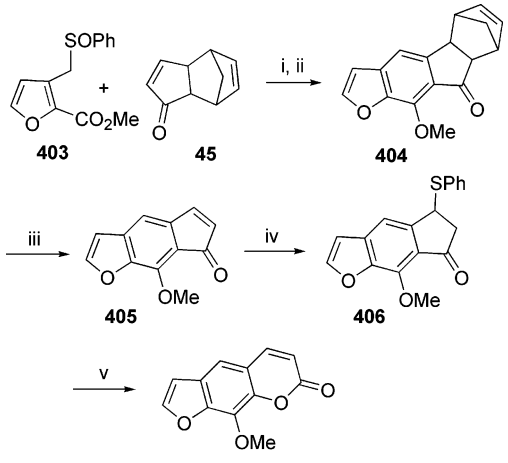
[a] Reagents and conditions: (i) LHMDS, THF, 0 °C. (ii) $PhI(OCOCF_3)_2$, THF, 0 °C. (iii) air, daylight, THF. (iv) $MgBr_2$, Et_2O; 15% overall yield.

Scheme 95[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C; 70%.

Scheme 96[a]

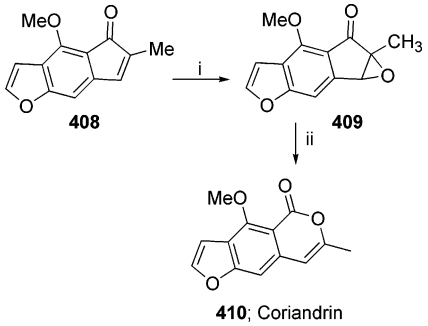


[a] Reagents and conditions: (i) LTB, −78 °C, THF; 73%. (ii) K_2CO_3, acetone, MeI; 96%. (iii) FVP (450 °C, 0.1 Torr); 98%. (iv) PhSH, Et_3N; 86%. (v) H_2O_2, Ac_2O, H_2SO_4; 15%.

403 and bicyclic enone **45**. This was then *O*-methylated and pyrolyzed to give furoindenone **405**, which was elaborated in two steps to pharmaceutically useful 8-methoxypsoralen (**407**).[133]

A similar strategy, when extended to the isomeric furan donor, yielded furoindenone **408**. In two steps, it was transformed, via an uncommon thermal rearrangement, to

Scheme 97[a]



[a] Reagents and conditions: (i) Et_3N, H_2O_2; 40%. (ii) FVP (450 °C, 0.1 Torr); 88%.

coriandrin (**410**), a naturally occurring furoisocoumarin (Scheme 97).[134]

10. Conclusions

There are not many annulations in the literature that are truly fundamental and useful. The Hauser annulation, on the other hand, is endowed with several attributes: (i) it is a one-pot operation, (ii) a large variety of substituents can be accommodated in both Hauser donors and acceptors, (iii) highly oxygenated anthraquinones can be prepared without an extra oxidation step, (iv) yields are normally very high under optimized conditions, and (v) many base-sensitive groups survive strongly basic reaction conditions since annulation takes place at low temperatures and the resultant anions are only weakly basic. The reaction is sufficiently mild and reliable to be used in the last or penultimate step of a total synthesis of a complex molecule.[50] Although the reaction was, for many years, largely focused on synthesis of anthracyclines and related aromatic polyketides, it found many new applications in the past 10 years. Its potential in the field of heterocyclic chemistry will be further studied and exploited. It can be expected that the reaction will be further refined and used more frequently in the synthesis of complex molecules like hibarimicins, signal transduction inhibitors,[135] and angelmicins.[136]

11. Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butoxycarbamoyl
CAN	cerium(IV) ammonium nitrate
Cbz	carboxybenzyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoramide
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide
KTB	potassium *tert*-butoxide
LDA	lithium diisopropylamide
LiHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazide
LTB	lithium *tert*-butoxide
LiTMP	lithium 2,2,5,5-tetramethylpiperidide
MCPBA	*m*-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
NaHMDS	sodium 1,1,1,3,3,3-hexamethyldisilazide
PIDA	phenyliodonium diacetate
Piv	2,2-dimethylpropanoyl (pivaloyl)
PMB	4-methoxybenzyl
PNB	4-nitrobenzyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA	4-toluenesulfonic acid
Py	pyridine
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethansulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

12. Acknowledgments

The authors gratefully acknowledge the continuous support of their research by DST, New Delhi, and CSIR, New Delhi, in the form of research grants and research fellowships. D.M. is thankful to his research scholars, Ranjan, Murty, Gita, Nirmal, Mausumi, Haren, Sujit, Satyajit, Asit, Bidyut, Sutapa, Saroj, Amit, and Indrajeet, who have contributed to the Hauser annulation by their original research.

13. References

(1) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) De Koning, C. B.; Rousseau, A. L.; Van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7.
(2) (a) Hayashi, M. *J. Chem. Soc.* **1927**, 2516. (b) Opitz, A.; Roemer, E.; Haas, W.; Gorls, H.; Werner, W.; Grafe, U. *Tetrahedron* **2000**, *56*, 5147.
(3) Vollhardt, K. P. C. *Angew. Chem., Int. Ed.* **1984**, *23*, 539.
(4) (a) Dotz, K. H. *Angew. Chem., Int. Ed.* **1984**, *23*, 587. (b) Wulff, W. D.; Liebeskind, L. S. *Advances in Metal-Organic Chemistry*; JAI Press Inc.: Greenwich, CT, 1989; Vol. 1.
(5) (a) Kita, Y.; Iio, K.; Kawaguchi, K. I.; Fukuda, N.; Takeda, Y.; Ueno, H.; Okunaka, R.; Higuchi, K.; Tsujino, T.; Fujioka, H.; Akai, S. *Chem. Eur. J.* **2000**, *6*, 3897. (b) Huang, K.-S.; Wang, E.-C. *Tetrahedron Lett.* **2001**, *42*, 6155. (c) Duan, Z.; Nakajima, K.; Takahashi, T. *Chem. Commun.* **2001**, 1672. (d) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *Tetrahedron Lett.* **1996**, *46*, 8277.
(6) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199.
(7) Alan, M. D.; Alison, J. H.; Guy, C. L.-J. *Synthesis* **2006**, 4093.
(8) (a) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065. (b) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (c) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.
(9) Asao, N. *Synlett* **2006**, 1645.
(10) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178.
(11) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
(12) Muller, P. *Pure Appl. Chem.* **1994**, *66*, 1077.
(13) Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1995**, *51*, 5207.
(14) Matsumoto, T.; Yamaguchi, H.; Tanabe, M.; Yasui, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8393.
(15) Mal, D.; Patra, A.; Roy, H. *Tetrahedron Lett.* **2004**, *45*, 7895.
(16) (a) Snider, B. B.; Gao, X. *J. Org. Chem.* **2005**, *70*, 6863. (b) Nicolaou, K. C.; Papageorgiou, C. D.; Piper, J. L.; Chadha, R. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5846. (c) Nicolaou, K. C.; Lim, Y. H.; Papageorgiou, C. D.; Piper, J. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 7917. (d) Nicolaou, K. C.; Lim, Y. H.; Piper, J. L.; Papageorgiou, C. D. *J. Am. Chem. Soc.* **2007**, *129*, 4001.
(17) Shair, M. D.; Yoon, T. Y.; Karoline, K. M.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509.
(18) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263.
(19) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Soc. Chim. Fr.* **1993**, *130*, 447.
(20) Hassner, A.; Stumer, C. *Organic Synthesis Based on Named reactions*; Elsevier Science: U.K., 2002; p 153.

(21) Couladouros, E. A.; Strongilos, A. T.; Papageoorgiou, V. P.; Plyta, Z. F. *Chem. Eur. J.* **2002**, *8*, 1795.
(22) Braukmuller, S.; Brückner, R. *Eur. J. Org. Chem.* **2006**, 2110.
(23) Brimble, M. A.; Houghton, S. I.; Woodgate, P. D. *Tetrahedron* **2007**, *63*, 880.
(24) Pesson, M. Belg. Patent 637049, 1963; *Chem. Abstr.* **1965**, *62*, 10412.
(25) Kraus, G.; Sugimoto, H. *Synth. Commun.* **1977**, *7*, 505.
(26) Kraus, G.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *19*, 2263.
(27) (a) Patai, S.; Rappport, Z. *The Chemistry of the Quinonoid Compounds*; John Wiley & Sons: New York, 1988. (b) Thomson, R. H. *Naturally Occurring Quinones III. Recent Advances;* Chapman and Hall: London, 1987.
(28) Jung, M. E; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.
(29) (a) Khanapure, S. P.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 5685. (b) Mal, D.; Senapati, B.; Pahari, P. *Synlett* **2005**, 994. (c) Mal, D.; Senapati, B.; Pahari, P. *Tetrahedron* **2007**, *63*, 3768.
(30) Evans, J. C.; Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1988**, *53*, 5519.
(31) Lebrasseur, N.; Fan, G.-J.; Oxoby, M.; Looney, M. A.; Quideau, S. *Tetrahedron* **2005**, *61*, 1551.
(32) Mal, D.; Ray, S.; Sharma, I. Submitted for publication.
(33) Hauser, F. M.; Yin, H. *Org. Lett.* **2000**, *2*, 1045.
(34) Li, T.-t.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *22*, 3741.
(35) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439.
(36) Ghorai, S. K.; Roy, H. N.; Bandopadhyay, M.; Mal, D. *J. Chem. Res. (S)* **1999**, 30.
(37) Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett.* **2002**, *4*, 2237.
(38) (a) Watanabe, M.; Morimoto, H.; Nogami, K.; Ijichi, S.; Furukawa, S. *Chem. Pharm. Bull.* **1993**, *41*, 968. (b) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493.
(39) Rho, Y. S.; Yoo, J. H.; Baek, B. N.; Kim, C. J.; Cho, I. H. *Bull. Korean Chem. Soc.* **1996**, *17*, 946.
(40) Katritzky, A. R.; Zhang, G.; Xie, L. *Synth. Commun.* **1997**, *27*, 3951.
(41) Dey, S. R.; Pahari, P.; Mal. D. Unpublished result.
(42) Warrener, R. N.; Liu, L.; Russell, R. A.; Tiekink, E. R. T. *Synlett* **1998**, 387.
(43) Hauser, F. M.; Liao, H.; Sun, Y. *Org. Lett.* **2002**, *4*, 2241.
(44) Piggott, M. J.; Wege, D. *Aust. J. Chem.* **2003**, *56*, 691.
(45) Cho, I. H.; Rho, Y. S.; Lee, J. Y.; Soh, S.; Kim, S.; Si, H.; Yoo, D.; Kim, S. I. *J. Korean Chem. Soc.* **1991**, *35*, 756.
(46) Rho, Y. S.; Yoo, J. H.; Kwon, Y. J.; Park, S. H.; Cho, I. H. *J. Korean Chem. Soc.* **1996**, *40*, 519.
(47) (a) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378. (b) Majetich, G.; Casres, A. M.; Chapman, D.; Behnke, M. *Tetrahedron Lett.* **1983**, *24*, 1909−1912.
(48) Mal, D.; Hazra, N. K.; Murty, K. V. S. N.; Majumdar, G. *Synlett* **1995**, 1239.
(49) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181.
(50) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921.
(51) Mal, D.; Hazra, N. K. *Tetrahedron Lett.* **1996**, *37*, 2641.
(52) Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722.
(53) Feldman, K. S.; Eastman, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 12562.
(54) Mal, D.; Hazra, N. K. *Chem. Commun.* **1996**, 1181.
(55) (a) Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1982**, *47*, 383. (b) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. (c) Hauser, F. M.; Chakrapani, S.; Ellengenberger, W. P. *J. Org. Chem.* **1991**, *56*, 5248. (d) Hauser, F. M.; Takeuchi, C.; Yin, H.; Corlett, S. A. *J. Org. Chem.* **1994**, *59*, 258.
(56) Crawley, M. L.; Hein, K. J.; Markgraf, J. H. *J. Chem. Res. (S)* **2003**, 470.
(57) Hauser, F. M.; Xu, Y. *Org. Lett.* **1999**, *1*, 335.
(58) Murty, K. V. S. N.; Hazra, N. K.; Datta, K.; Mal, D. *Indian J. Chem.* **1997**, *36B*, 126.
(59) Rho, Y. S.; Park, S. H.; Kim, M. S.; Yun, Y. K.; Cho, I. H.; Kang, H. S. *Bull. Korean Chem. Soc.* **1994**, *15*, 360.
(60) Yamaguchi, H.; Konegawa, T.; Tanabe, M.; Nakamura, T.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8389.
(61) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844.
(62) (a) Mal, D.; Roy, H. N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3167. (b) Similar reactions with phenylsulfonylphthalides (e.g., **1**) did not occur possibly due to the steric bulk of the phenylsulfonyl group.
(63) Wang, J.; Pettus, L. H.; Pettus, T. R. R. *Tetrahedron Lett.* **2004**, *45*, 1793.
(64) (a) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, *105*, 5688. (b) Hauser, F. M.; Mal, D. U.S. Patent 4,515,720, 1985; *Chem. Abstr.* **1985**, *103*, 123268w.
(65) Tatsuta, K.; Inukai, T.; Itoh, S.; Kawarasaki, M.; Nakano, Y. *J. Antibiot.* **2002**, *55*, 1076.
(66) (a) Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984**, *40*, 4711. (b) Rho, Y. S.; Kim, S. Y.; Cho, I.; Kang, H. S.; Yoo, D. J.; Cheong, C. J. *Bull. Korean Chem. Soc.* **1998**, *19*, 1059. (c) Rho, Y. S; Choi, Y.; Kim, G.; Sin, H.; Yoo, D. J.; Kim, S. H.; Cheong, C. *Bull. Korean Chem. Soc.* **1999**, *20*, 551.
(67) (a) Freskos, J. N.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1985**, 658. (b) Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699.
(68) Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.* **1990**, *31*, 5495.
(69) Hoffmann, B.; Lackner, H. *Liebigs Ann. Chem.* **1995**, 87.
(70) Nomura, K.; Okazaki, K.; Horo, K.; Yoshii, E. *J. Am. Chem. Soc.* **1987**, *109*, 3402.
(71) Claessens, S.; Naidoo, D.; Mulholland, D.; Verschaeve, L.; Van Staden, J.; De Kimpe, N. *Synlett* **2006**, 621.
(72) (a) Swenton, J. S.; Freskos, J. N.; Dalidowicz, P.; Kerns, M. L. *J. Org. Chem.* **1996**, *61*, 459. (b) Deshpande, P. P.; Price, K. N.; Baker, D. C. *J. Org. Chem.* **1996**, *61*, 455.
(73) Tatsuta, K.; Hirabayashi, T.; Kojima, M.; Suzuki, Y.; Ogura, T. *J. Antibiot.* **2004**, *57*, 291.
(74) Couladouros, E. A.; Strongilos, A. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3677.
(75) Tatsuta, K.; Tanaka, Y.; Kojima, M.; Ikegami, H. *Chem. Lett.* **2002**, 14.
(76) Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 4515.
(77) Dodsworth, D. J.; Calcagno, M.-P.; Ehrmann, E. U.; Devadas, B.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2120.
(78) Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1981**, 108.
(79) Zhao, H.; Biehl, E. *J. Nat. Prod.* **1995**, *58*, 1970.
(80) Han, W.; Tran, J.; Zhang, H. M.; Jeffrey, S.; Swartling, D.; Ford, G. P.; Biehl, E. *Synthesis* **1995**, 827.
(81) Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H. G. *Tetrahedron* **2003**, *59*, 3201.
(82) Majumdar, G.; Murty, K. V. S. N.; Mal, D. *Tetrahedron Lett.* **1994**, *35*, 6139.
(83) Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413.
(84) (a) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625−4632. (b) Bennani, F.; Florent, J.-C.; Koch, M.; Monneret, C. *Tetrahedron Lett.* **1984**, *25*, 3975−3978. (c) Keay, B. A.; Rodrigo, R. *Tetrahedron* **1984**, *40*, 4597−4607.
(85) Ge, P.; Russell, R. A. *Tetrahedron* **1997**, *53*, 17477.
(86) Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 4387.
(87) Mal, D.; Roy, H. N.; Hazra, N. K.; Adhikary, S. *Tetrahedron* **1997**, *53*, 2177.
(88) Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett.* **2002**, *4*, 2237.
(89) Tso, H.-H.; Chen, Y.-J. *J. Chem. Res. (S)* **1995**, 104.
(90) Lipshutz, B. H.; Mollard, P.; Pfeiffer, S. S.; Chrisman, W. *J. Am. Chem. Soc.* **2002**, *124*, 14282.
(91) Patra, A.; Pahari, P.; Ray, S.; Mal, D. *J. Org. Chem.* **2005**, *70*, 9017.
(92) Marsden, R.; MacLean, D. B. *Can. J. Chem.* **1984**, *62*, 1392.
(93) Swenton, J. S.; Bonke, B. R.; Clark, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.* **1990**, *55*, 2077.
(94) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.
(95) Yoon, T. Y.; Shair, M. D.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 6259.
(96) Ng, W.; Wege, D. *Tetrahedron Lett.* **1996**, *37*, 6797.
(97) (a) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774. (b) Brade, W.; Vasella, A. *Helv. Chim. Acta* **1989**, *72*, 1649.
(98) Patra, A.; Mal, D. Unpublished results.
(99) Mal, D.; Pal, R.; Murty, K. V. S. N. *J. Chem. Soc., Chem. Commun.* **1992**, 821.
(100) Majumdar, G.; Pal, R.; Murty, K. V. S. N.; Mal, D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 309.
(101) (a) Alguacil, R.; Farina, F.; Martin, M. V.; Paredes, M. C. *Tetrahedron Lett.* **1995**, *36*, 6773. (b) Alguacil, R.; Martin, M. V.; Paredes, M. C. *Heterocycles* **2000**, *53*, 1029.
(102) Hauser, F. M.; Dorsch, W. A. *Org. Lett.* **2003**, *5*, 3753.
(103) Hauser, F. M.; Gauuan, P. J. F. *Org. Lett.* **1999**, *1*, 671.
(104) Angle, S. R.; Rainier, J. D.; Woytowicz, C. *J. Org. Chem.* **1997**, *62*, 5884.
(105) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.
(106) Asenjo, P.; Farina, F.; Martin, M. V.; Paredes, M. C.; Soto, J. J. *Tetrahedron* **1997**, *53*, 1823.
(107) Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 2356.
(108) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318.
(109) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.
(110) Mal, D.; Dey, S. *Tetrahedron* **2006**, *62*, 9589.
(111) Murty, K. V. S. N.; Pal, R.; Datta, K.; Mal, D. *Synth. Commun.* **1990**, *20*, 1705.
(112) Meyers, A. I.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881.

(113) Russell, R. A.; Pilley, B. A.; Warrener, R. N. *Synth. Commun.* **1986**, *16*, 425.
(114) Li, T.-t.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7007.
(115) Okazaki, K.; Nomura, K.; Yoshii, E. *Synth. Commun.* **1987**, *17*, 1021.
(116) Russell, R. A.; Warrener, R. N. *Tetrahedron Lett.* **1986**, *27*, 3431.
(117) Matsumoto, T.; Yamaguchi, H.; Hamura, T.; Tanabe, M.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8383.
(118) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589.
(119) Napolitano, E.; Spinelli, G.; Fiaschi, R.; Marsili, A. *Synthesis* **1985**, 38.
(120) Watanabe, M.; Furukawa, S. *Synlett* **1991**, 481.
(121) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061.
(122) Achmatowicz, O.; Szechner, B. *J. Org. Chem.* **2003**, *68*, 2398.
(123) Russell, R. A.; Pilley, B. A.; Irvine, B. A.; Warrener, R. N. *Aust. J. Chem.* **1987**, *40*, 311.
(124) Mitchell, A. S.; Russell, R. A. *Tetrahedron Lett.* **1993**, *34*, 545.
(125) Pahari, P.; Senapati, B.; Mal, D. *Tetrahedron Lett.* **2007**, *48*, 2635.
(126) Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162.
(127) Kobayashi, K.; Maeda, K.; Uneda, T.; Morikawa, O.; Konishi, H. *J. Chem. Soc., Perkin Trans 1* **1997**, 443.
(128) Magnus, P.; Eisenbeis, S. A.; Magnus, N. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1545.
(129) Mal, D.; Senapati, B.; Pahari, P. *Tetrahedron Lett.* **2006**, *47*, 1071.
(130) Lio, K.; Ramesh, N. G.; Okajima, A.; Higuchi, K.; Gujioka, H.; Akai, S.; Kita, Y. *J. Org. Chem.* **2000**, *65*, 89.
(131) Shair, M. D.; Yoon, T. Y.; Karoline, K. M.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509.
(132) Patra, A.; Ghorai, S. K.; De, S. R.; Mal, D. *Synthesis* **2006**, 2556.
(133) Mal, D.; Murty, K. V. S. N.; Datta, K. *Tetrahedron Lett.* **1994**, *35*, 9617.
(134) Mal, D.; Bandyopadhyay, M.; Ghorai, S. K.; Datta, K. *Tetrahedron Lett.* **2000**, *41*, 3677.
(135) Hori, H.; Igarashi, Y.; Kajiura, T.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oka, T. *J. Antibiot.* **1998**, *51*, 402.
(136) Uehara, Y.; Li, P.-M.; Fukazawa, H.; Mizuno, S.; Nihei, Y.; Nishio, M.; Hanada, M.; Yamamoto, C.; Furumai, T.; Oki, T. *J. Antibiotics* **1993**, *46*, 1306.

CR068398Q