Synlett R. A. Fernandes et al. Account

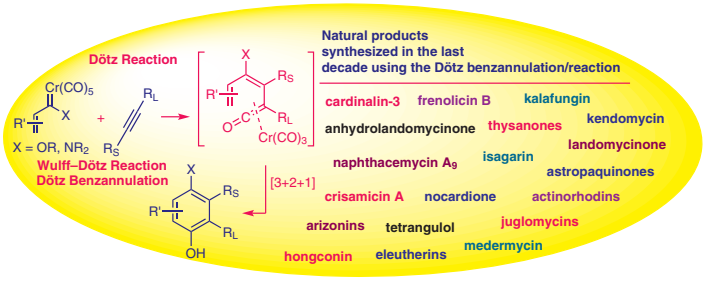
A Decade with Dötz Benzannulation in the Synthesis of Natural Products

Rodney A. Fernandes* 
Anupama Kumari‡
Ramdas S. Pathare‡

Department of Chemistry, Indian Institute of Technology Bombay, Powai Mumbai 400076, Maharashtra, India
rfernand@chem.iitb.ac.in

‡ These authors contributed equally

Dedicated to Professor Reinhard Brückner (Albert-Ludwigs University Freiburg) on the occasion of his 64th birthday



Received: 08.12.2019
Accepted after revision: 29.12.2019
Published online: 03.02.2020
DOI: 10.1055/s-0039-1690791; Art ID: st-2019-a0661-a

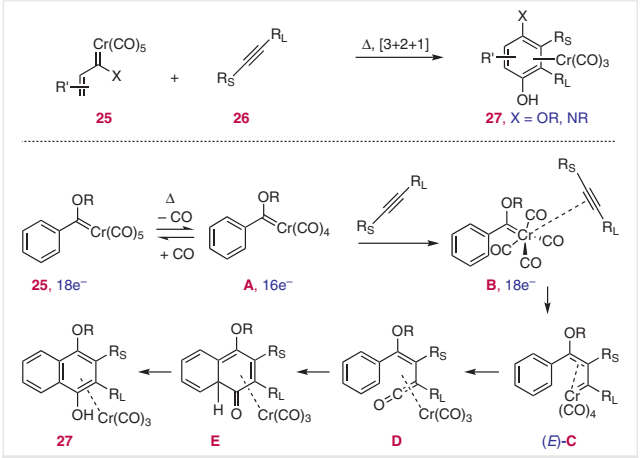
Abstract The Dötz benzannulation is a named reaction that utilizes Fischer chromium carbenes in a formal [3+2+1] cycloaddition with an alkyne and CO to produce the corresponding benzannulated product. Since its development in the 1970s, this reaction has been extensively used in the synthesis of natural products and various molecular architectures. Although the reaction sometimes suffers from the formation of other competing side products, the rapid construction of naphthol structures with a 1,4-dihydroxy unit makes it the most appropriate reaction for the synthesis of *p*-naphthoquinones. This review focuses on our group's efforts over the past decade on the extensive use of this annulation reaction along with the contributions of others on the synthesis of different natural products.

Key words Dötz benzannulation, natural products, cycloaddition, Fischer carbenes, naphthoquinones

1 Introduction

Natural products synthesis has remained one of the most exciting and dynamic global enterprises in research and has continued to inspire many researchers and practitioners to develop efficient strategies that resemble Nature's intriguing ways of making molecules.[1] Natural products have been used from ancient times in Ayurveda as traditional folk medicines, as well in the modern era as drugs, and many of them are utilized in lead development to meet the ever-growing need for new pharmaceuticals and therapeutic drugs.[2] Therefore, interest in the synthesis of natural products and analogues for bioactivity studies goes unabated. Many natural products fall in the classes of naphthoquinones,[3–6] decorated with various other functionalities. However, there are only a handful of methods available for the direct synthesis of naphthalene molecules with a 1,4-dihydroxy unit that can be converted into naphthoquinones. The Dötz benzannulation[7–9] and Hauser–Kraus annulation[10] are front runners for the rapid generation of naphthoquinone units and hence their application in naphthoquinone natural products synthesis is highly commendable and well-recognized by the synthetic community.

Since its discovery in 1975, the Dötz benzannulation or Dötz reaction has been extensively used in natural products synthesis, especially complex phenolic compounds, e.g., vitamins,[11a,b] daunomycinone,[11c–g] menogaril,[11h,i] olivine,[12a–c] fredricamycin,[13] pyranonaphthoquinones,[14] steroids,[15] kendomycin,[16] etc. Wulff has explored various facets of this re-



Scheme 1 A general reaction and a plausible mechanism for the Dötz benzannulation

© 2020. Thieme. All rights reserved.
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

action including mechanistic studies and one of the important contributions from his group was the use of this reaction to synthesize calixarenes.[9g]

We have previously reviewed the strategic use of this reaction for the preparation of functionalized and chiral calixarenes.[9g] Due to Wulff's significant contribution in this field, the reaction is also now called the Wulff–Dötz reaction. The reaction involves a thermal [3+2+1] benzannulation of α,β-unsaturated Fischer carbenes with alkynes involving an in situ incorporation of CO to provide the naphthol moiety.[9] While extensive contributions using this reaction have been reviewed earlier,[7b,9c,d,f,g,j] over the last one decade our group (Figure 1) and others (Figure 2) have contributed extensively toward the synthesis of naphthoquinone and related natural products. The somewhat limited growth in use of this reaction can be attributed to the toxicity associated with chromium. This review focuses on recent investigations over the last decade on the use of the Dötz benzannulation reaction in natural products synthesis.

2 General Description and Mechanism of the Dötz Benzannulation Reaction

The Dötz benzannulation or Dötz reaction, discovered by K. H. Dötz in 1975,[7a] is a thermal [3+2+1] annulation reaction of α,β-unsaturated Fischer carbene complexes (aromatic or vinylic)[17] with alkynes and involves the incorporation of a CO molecule to produce a phenol or the naphthol. The reaction is also referred to as the Dötz annulation and more recently as the Wulff–Dötz reaction. The most accept-

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Biographical Sketches

Rodney A. Fernandes completed his Ph.D. in organic chemistry at the CSIR-National Chemical Laboratory, Pune, India, under the guidance of Dr. Pradeep Kumar. He subsequently undertook postdoctoral research at Tohoku University, Japan with Prof. Yoshinori Yamamoto, followed by a period as an Alexander von Humboldt fellow and then a DFG postdoctoral fellow at the University of Freiburg with Prof. Reinhard Brückner. He started his independent research at the Instituto de Quimica, UNAM, Mexico City (Sep 2006 to July 2007). He then joined the Department of Chemistry, Indian Institute of Technology Bombay (IIT-Bombay), India as an assistant professor in August 2007 and became a full professor in May 2015. His research interests include asymmetric synthesis, total synthesis and the development of new synthetic methodologies. He was a recipient of the INSA medal for Young Scientists in Chemical Sciences in 2004 and has been an Elected Fellow of the Maharashtra Academy of Sciences since 2015. He received a Departmental Excellence in Teaching Award 2019–2020 from IIT Bombay.

Anupama Kumari received her B.Sc. (2011) and M.Sc. (2013) degrees in organic chemistry from Patna University, Patna, India. She passed her CSIR NET in December 2014 and her GATE exam in 2015 and joined the research group of Prof. Rodney A. Fernandes at the Department of Chemistry, IIT-Bombay, India in December 2015 as a Ph.D. student with institute fellowship. Her research focuses on the development of new methodologies and the synthesis of biologically active natural products.

Ramdas S. Pathare received his B.Sc. (2009) and M.Sc. (2011) degrees in organic chemistry from the University of Pune, Maharashtra, India. He was awarded his Ph.D. in 2019 from the Central University of Rajasthan, India under the supervision of Dr. Devesh M. Sawant. He then moved to the Indian Institute of Technology, Bombay (IIT-Bombay), India where he is presently working as a postdoctoral researcher in the laboratory of Prof. Rodney A. Fernandes. His current research is focused on the development of new synthetic methodologies for the synthesis of complex heterocycles and biologically active natural products.

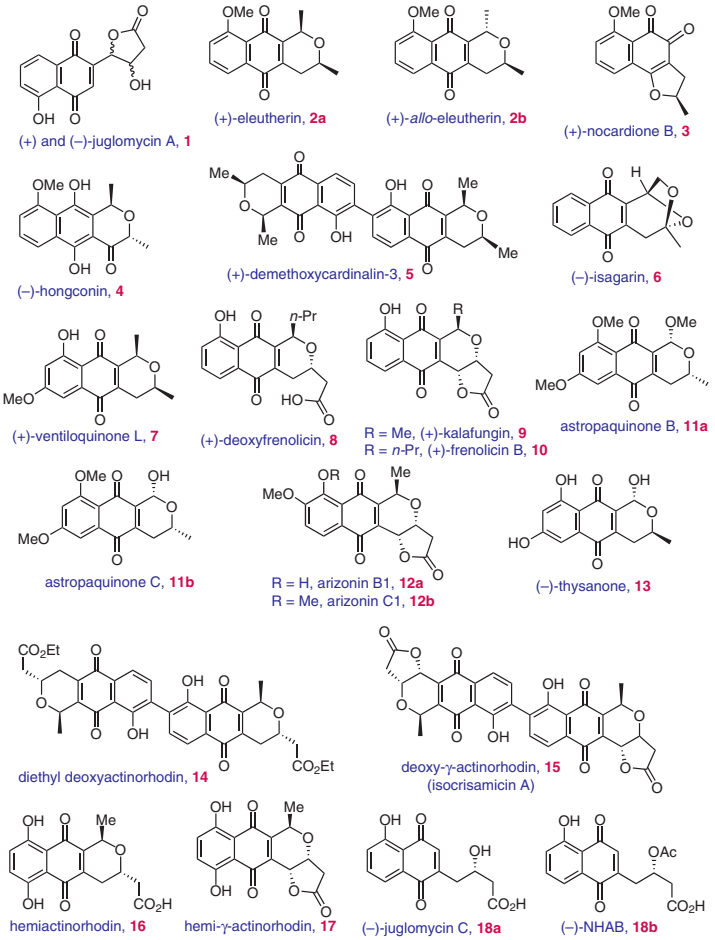


Figure 1 Natural products and analogues synthesized by our group in the last decade using the Dötz benzannulation as a key step

ed mechanism for this reaction is depicted in Scheme 1.[9f] Under mild thermal conditions, the rate-determining step is reversible dissociation of CO from the 18e⁻ pentacarbonylcarbene complex **25** to give the reactive, coordinatively unsaturated 16e⁻ tetracarbonylcarbene complex **A**. Insertion of an alkyne into the carbene furnishes the metallatriene (*Z*)- or (*E*)-**C** via intermediate **B**. The insertion of CO into carbene (*E*)-**C** generates the highly reactive ketene intermediate **D**, which undergoes nucleophilic attack to give **E**, which is followed by aromatization to afford the chromium tricarbonyl coordinated complex **27**. The product naphthol is released after air oxidation. The reaction occurs with good regioselectivity for the alkyne substituents. In the intermediate **B**, the alkyne insertion occurs by keeping the larger group away from the carbene alkoxy group resulting in it being placed *ortho* to the phenol.[18] The optimum conditions identified for the benzannulation involve the reaction being carried out in *n*-heptane at a 0.3 M concentration of the chromium complex and with a slight excess of the alkyne (1.0–1.5 equiv).[18a] The success of the benzannulation over other side-product formation relies on the geometry of the metallatriene intermediate with the (*E*)-isomer undergoing cyclization through carbonyl insertion. However, the (*Z*)-metallatriene leads to furan products. Wulff and co-workers have carried out a study of the stereoelectronic effects for (*E*)- or (*Z*)-metallatriene formation.[9b] The carbonyl insertion is also crucial to obtain the ketene intermediate **D**, which undergoes aromatic electrophilic substitution leading to phenol formation. On the other hand, a direct electrocyclic ring closure in **C** affords the indene products (not shown).[19]

3 Applications of the Dötz Benzannulation Reaction in Natural Products Synthesis over the Last Decade

The Dötz benzannulation has been steadily used over the last decade in the synthesis of various natural products (Figures 1 and 2). While there have been previous reviews covering different aspects of this reaction, in this review, its

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

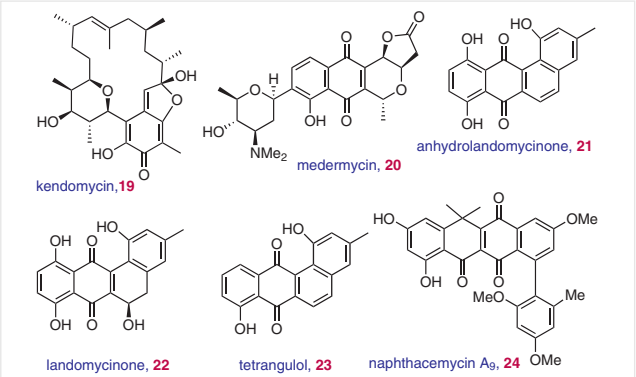


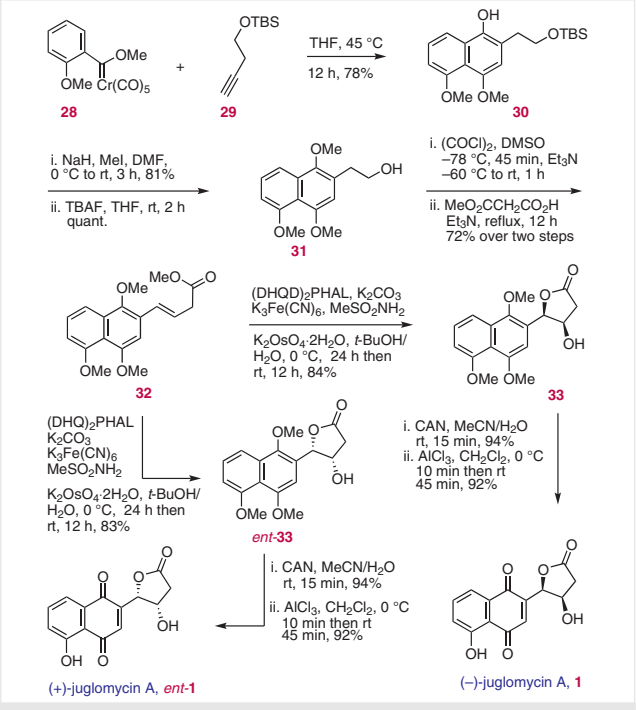
Figure 2 Natural products synthesized by other groups over the last decade using the Dötz benzannulation as a key step

strategic use in natural products synthesis has been abstracted from 2008 onwards.

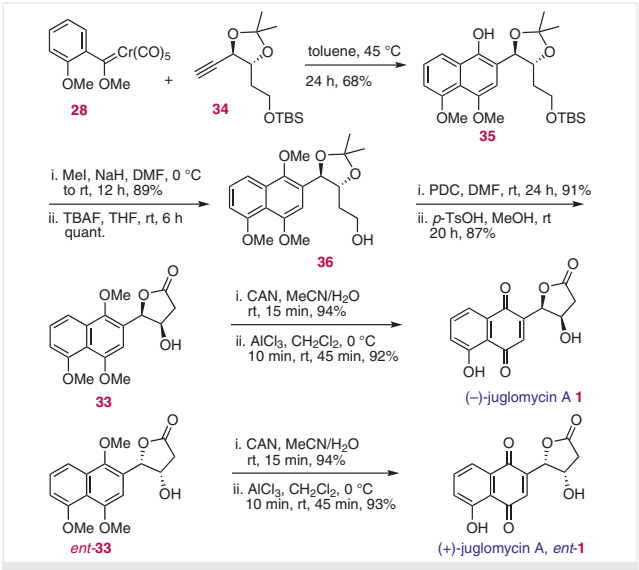
3.1 Synthesis of (+) and (–)-Juglomycin A (1)[20,21]

We started working in the area of the strategic use of the Dötz benzannulation reaction in natural products synthesis back in 2008, with the first installment of our work disclosing the synthesis of both enantiomers of juglomycin A (**1**).[20] This compound was isolated from the culture filtrate of the fungus *Streptomyces* sp. 190–2 and shows antitumor as well as antibacterial activities against both Gram-negative and Gram-positive bacteria.[22] Both enantiomers of juglomycin A were synthesized utilizing the Dötz benzannulation reaction (Scheme 2). To begin with, the condensation of Fischer carbene complex **28**[11d] with alkyne **29**[23] afforded the Dötz benzannulated product **30** in a good yield of 78%. Methylation of the phenolic hydroxy group with MeI and TBS deprotection provided **31** in 81% yield (two steps). Swern oxidation of **31** to the corresponding aldehyde and condensation with the half ester of malonic acid under decarboxylative–deconjugative–Knoevenagel conditions[24] gave the β,γ-unsaturated ester **32** in 72% yield (over two steps). Sharpless asymmetric dihydroxylation[25] of **32** with the $(DHQD)_2PHAL$ ligand afforded β-hydroxy-γ-lactone **33** in 84% yield and an excellent enantioselectivity of 99.5% ee. Treatment of **33** with cerium(IV) ammonium nitrate (CAN) gave the quinone (94%) and demethylation with $AlCl_3$ afforded (–)-juglomycin A (**1**) in 92% yield. Similarly, the unnatural enantiomer *ent*-1 was synthesized from **32** through asymmetric dihydroxylation using the $(DHQ)_2PHAL$ ligand to give *ent*-**33** in 83% yield and 98.5% ee. Quinone formation and demethylation gave (+)-juglomycin A (*ent*-**1**).

Later in 2011, we considered an alternative synthesis of (+)- and (–)-juglomycin A (**1**) using a functionalized alkyne (Scheme 3).[21] The reaction of Fischer carbene **28** with alkyne **34** gave the naphthol **35** in 68% yield. Methylation of the naphthol and TBS group removal furnished the alcohol **36**. Oxidation of the latter to the acid and lactonization then gave the lactone **33**. Finally, quinone formation and demethylation provided (–)-juglomycin A (**1**). Similarly, the use of the alkyne *ent*-**34** led to (+)-juglomycin A (*ent*-**1**).



Scheme 2 Synthesis of (+)- and (–)-juglomycin A



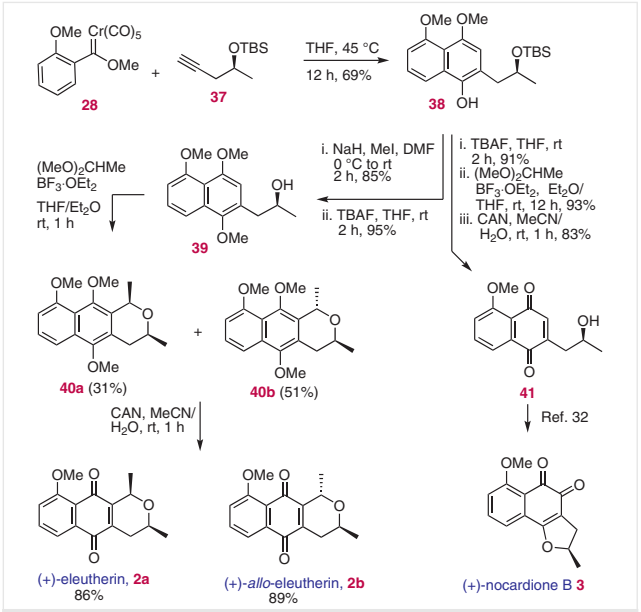
Scheme 3 An alternative synthesis of (+)- and (–)-juglomycin A

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

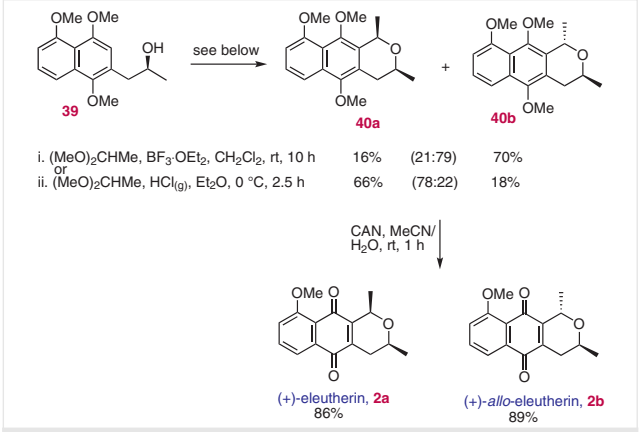
3.2 Synthesis of (+)-Eleutherin (2a), (+)-*allo*-Eleutherin (2b)and a Formal Synthesis of (+)-Nocardione B (3)[26,27]

We have also considered concise enantioselective syntheses of (+)-eleutherin (**2a**) and (+)-*allo*-eleutherin (**2b**) as well as the formal synthesis of (+)-nocardione B (**3**) (Scheme 4). (+)-Eleutherin (**2a**) and (–)-isoeleutherin (*ent*-**2b**) were isolated from the bulbs of *Eleutherin bulbosa*[28] in 1950. Eleutherin shows activity against *Bacillus subtilis*.[29] Extracts of *Eleutherin americana*, of which eleutherin and isoeleutherin are the major constituents, have been used to treat the heart disease angina pectoris.[30] (–)-Nocardione B (*ent*-**3**), showing moderate antifungal and cytotoxic activities, was isolated by Otani et al. in 2000 as a new tyrosine phosphate inhibitor.[31] Toward their synthesis, the Fischer carbene complex **28** was condensed with the chiral alkyne **37** via the Dötz benzannulation reaction to give the naphthol **38** in 69% yield (Scheme 4). Deprotection of the TBS group and an oxa-Pictet–Spengler reaction with $(MeO)_2CHMe$ gave the 7-membered cyclic acetal in 93% yield with the phenolic OH group involved. This on reaction with CAN resulted in the quinone **41** in 83% yield. The conversion of quinone **41** into (+)-nocardione B (**3**) has already been reported in the literature.[32] Hence, this work describes the formal synthesis of (+)-nocardione B (**3**). For the synthesis of eleutherin and *allo*-eleutherin, the phenolic OH in **38** was protected to give the methyl ether and TBS group removal then gave **39**. The subsequent oxa-Pictet–Spengler reaction provided a mixture of **40a**/**40b** in a 36:64 ratio. This mixture was separated by preparative TLC and oxidation with CAN produced (+)-eleutherin (**2a**) and (+)-*allo*-eleutherin (**2b**), respectively.

An improved synthesis of (+)-eleutherin (**2a**) and (+)-*allo*-eleutherin (**2b**) was subsequently reported by us (Scheme 5).[27] The intermediate **39** was prepared as reported by us earlier (Scheme 4). With the success in obtaining the *cis*-isomer in the synthesis of demethoxycardinalin-3 using dry HCl gas[33] (this work is discussed later), we considered similar conditions for the synthesis of eleutherin, aiming for either diastereomer to be obtained as the major product. Thus, the reaction of **39** with $(MeO)_2CHMe/BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 10 hours gave a mixture of **40a**/**40b** in a 21:79 ratio and isolated yields of 16% and 70%, respectively. However, the reaction by bubbling dry HCl gas through the mixture of **39** and $(MeO)_2CHMe$ in Et_2O at 0 °C for 2.5 hours provided a switched diastereoselectivity for **40a**/**40b** with a 78:22 ratio and isolated yields of 66% and 18%, respectively. The separated diastereomers on CAN oxidation gave (+)-eleutherin (**2a**) and (+)-*allo*-eleutherin (**2b**) in 86% and 89% yields, respectively.



Scheme 4 Synthesis of (+)-eleutherin (**2a**), (+)-*allo*-eleutherin (**2b**) and (+)-nocardione B (**3**)



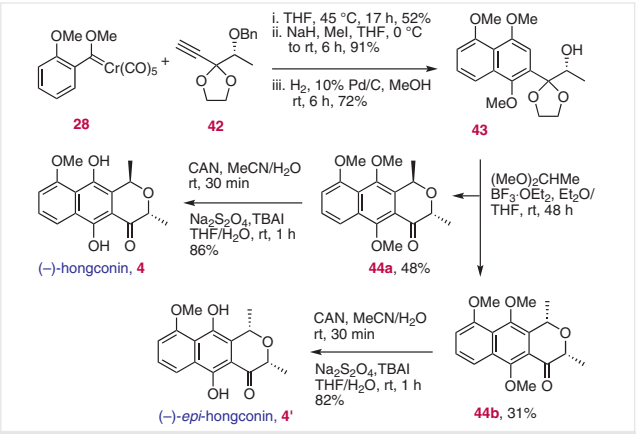
Scheme 5 An improved synthesis of (+)-eleutherin (**2a**) and (+)-*allo*-eleutherin (**2b**)

3.3 Synthesis of (–)-Hongconin (4)and (–)-1-*epi*-Hongconin (4′)[34]

(–)-Hongconin (**4**) was isolated from the rhizomes of *Eleutherine americana* by Chen and co-workers.[35] Pharmacological studies showed that hongconin enhanced the blood flow of coronary arteries and also reduced chest pain.[36] Our group has completed a concise enantioselective synthesis of both (–)-hongconin (**4**) and (–)-*epi*-hongconin (**4′**) (Scheme 6).[34] The Fisher carbene complex **28** was reacted with the alkyne **42** in a Dötz benzannulation reaction to provide the corresponding substituted naphthol, which on methylation of the phenolic OH followed by benzyl deprotection gave **43**. An oxa-Pictet–Spengler reaction of **43** with

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

$(MeO)_2CHMe/BF_3{\cdot}OEt_2$ furnished a mixture of **44a**/**44b** in a 3:2 ratio that was separated in 48% and 31% yields, respectively. Advantageously, the ketal group also underwent deprotection in this reaction. Subsequent CAN oxidation to the quinone and reduction with sodium dithionate gave (–)-hongconin (**4**). Similarly, CAN oxidation of **44b** and sodium dithionate reduction produced non-natural (–)-*epi*-hongconin (**4′**).

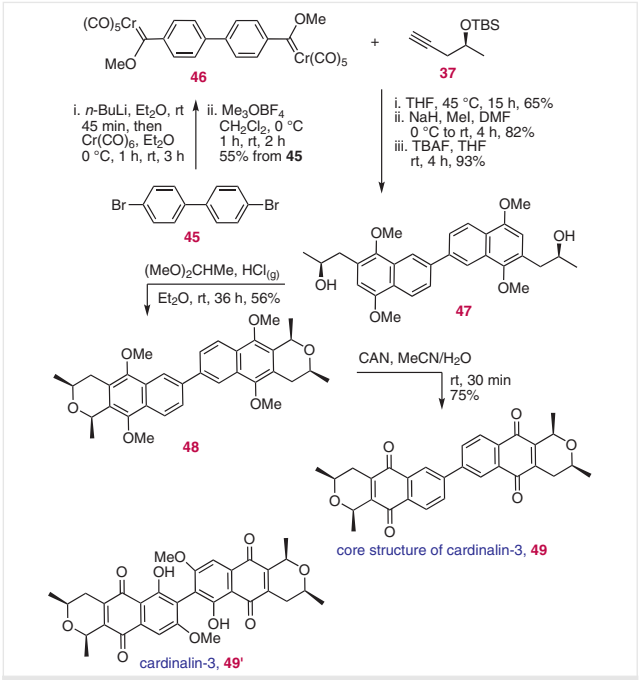


Scheme 6 Synthesis of (–)-hongconin (**4**) and (–)-*epi*-hongconin (**4′**)

3.4 Synthesis of the Regioisomeric Core Structure of Cardinalin-3 (49)[37] and Demethoxycardinalin-3 (5)[33]

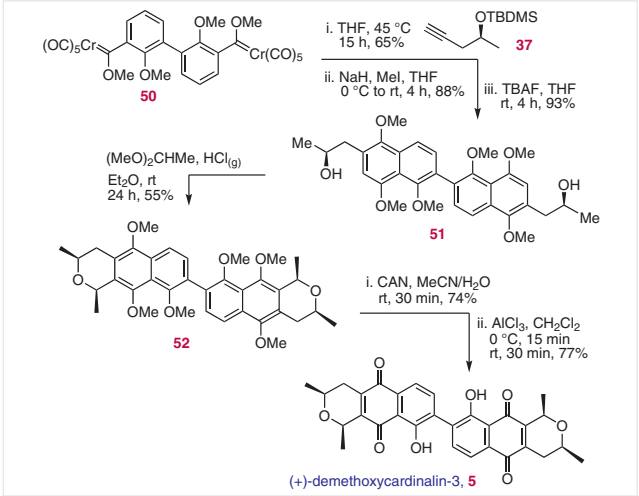
The cardinalins are a series of cytotoxic dimeric pyranonaphthoquinones isolated from the New Zealand toadstool *Dermocybe cardinalis*.[38] An ethanolic extract of the latter inhibits the growth of P388 murine leukemia cells (IC_{50} = 0.47 μg/mL).[38b] We executed a bidirectional Dötz benzannulation and oxa-Pictet–Spengler strategy toward the dimeric core structure of cardinalin-3 (**49′**) (Scheme 7). The dimeric Fischer carbene **46** (prepared from **45**) on reaction with alkyne **37** gave the dimer naphthol, which on methylation and TBS deprotection provided **47**. A subsequent oxa-Pictet–Spengler reaction using $(MeO)_2CHMe/BF_3{\cdot}OEt_2$ gave a mixture of *anti*/*anti* and *syn*/*anti* dimeric pyran products, while the *syn*/*syn* diastereomer was the desired intermediate. Fortunately, bubbling dry HCl gas into the oxa-Pictet–Spengler reaction mixture gave the desired *syn*/*syn*-pyran **48** along with the *syn*/*anti* diastereomer (not shown), which were obtained in 56% and 16% isolated yields, respectively. CAN oxidation of the former gave the dimeric core structure **49** (75%) of cardinalin-3 (**49′**).

The bidirectional Dötz benzannulation strategy was then extended to complete the total synthesis of demethoxycardinalin-3 (**5**) (Scheme 8).[33] The Fischer carbene **50** and alkyne **37** reacted to give the dimeric naphthol, which on methylation and TBS removal gave **51**. Subsequent oxa-Pictet–Spengler reaction under our successful HCl(g)[37] bubbling conditions gave the desired *syn*/*syn*-pyran product **52**



Scheme 7 Synthesis of the core structure **49** of cardinalin-3

along with the *syn*/*anti* diastereomer (not shown), obtained in 55% and 22% isolated yields, respectively. CAN oxidation of **52** and demethylation with $AlCl_3$ furnished demethoxycardinalin-3 (**5**). This structure represents the closest chiral analogue synthesized for cardinalin-3 (**49′**) in the literature.



Scheme 8 Total synthesis of (+)-demethoxycardinalin-3 (**5**)

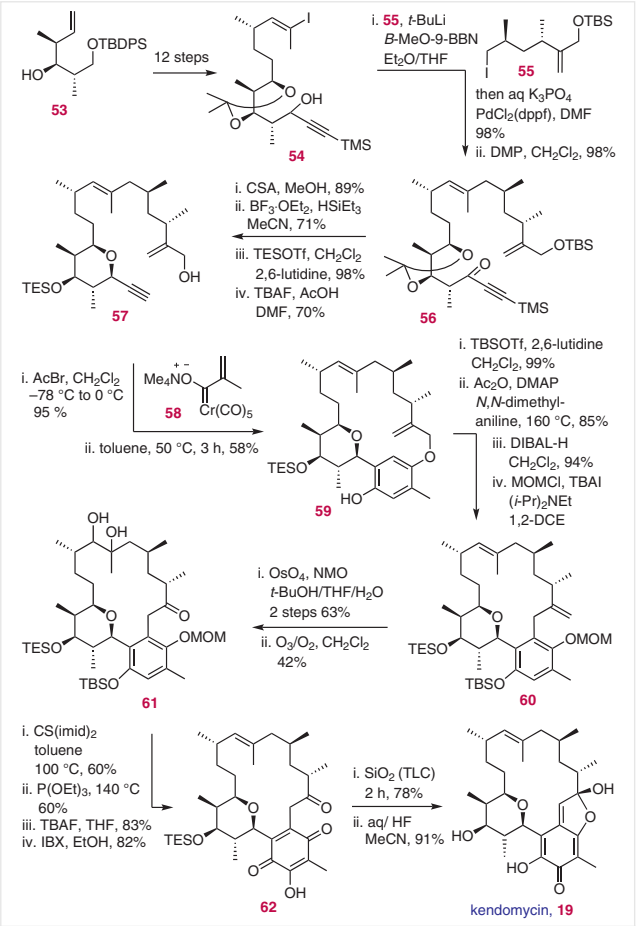
3.5 Total Synthesis of Kendomycin (19)[39]

Kendomycin (**19**), isolated from *Streptomyces* species, possesses an interesting ansa-type quinone methide framework which is directly fused with a substituted tetrahydropyran moiety and shows promising antibacterial and cyto-

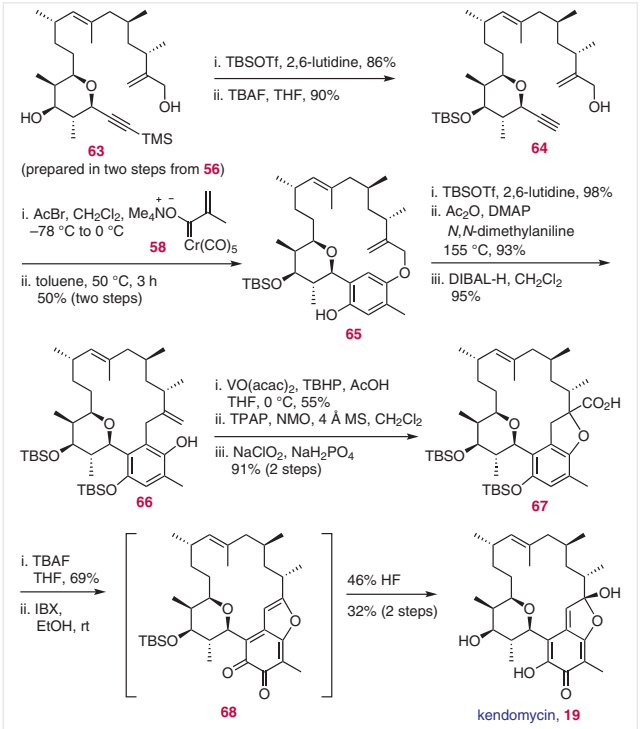
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

toxic activities.[40] Nakata and co-workers have described a challenging synthesis of kendomycin using an intramolecular Dötz reaction (Scheme 9). The synthesis commenced with the preparation of intermediate **54** from known alcohol **53**[41] in 12 steps. Meanwhile, compound **55** was prepared from *ent*-**53**[42] in 10 steps.[39a] The Pd-catalyzed Suzuki–Miyaura cross-coupling of **54** with **55** followed by alcohol oxidation generated the ynone **56**. Next, the ynone was subjected to acetal exchange followed by deoxygenation, then hydroxy protection as the TES ether and TMS/TBS removal gave the terminal alkyne **57**. In the next step, the carbene **58** was anchored to the alcohol **57** and then subjected to an intramolecular Dötz reaction to produce the phenol **59** in 58% yield. Silyl protection of the phenol and aryl-Claisen rearrangement in the presence of Ac_2O/DMAP gave the aryl acetate that was reduced back to the phenol and then protected as MOM ether **60**. The electron-rich internal double bond was masked as a diol and subsequent cleavage of the terminal double bond using O_3 gave the ketone **61**. Regeneration of the internal olefin and silyl deprotection furnished the phenol that was oxidized to the 2-hydroxy-1,4-quinone with IBX resulting in **62**. Finally, formation of the quinone methide on silica gel treatment and desilylation gave kendomycin (**19**). The synthesis was completed in 32 steps from known intermediate **53**.

In a subsequent paper, Nakata and co-workers[39b] studied the simultaneous macrocyclization and intramolecular Dötz benzannulation reaction for construction of the ansa structure, thereby preparing some analogues and completing a new synthesis of kendomycin (**19**) (Scheme 10). The previous synthesis (Scheme 9) required masking of the more reactive double bond for the oxidative cleavage of the terminal double bond. The new synthesis varied at this point and at the end. Compound **63**, obtained in the first two steps from **56** (see Scheme 9), on TBS protection gave the bis-TBS compound and selective removal of the primary TBS and the TMS groups gave **64**. A similar intramolecular Dötz benzannulation as before led to phenol compound **65** (this differs from **59** in having a TBS group). Subsequent TBS protection of the phenol and aryl-Claisen rearrangement in the presence of Ac_2O/DMAP gave the aryl acetate that was reduced back to phenol **66**. The latter on hydroxy-directed epoxidation also opened the epoxide to give a 2,3-dihydrobenzofuran with a primary alcohol that was oxidized to the acid **67**. Removal of the TBS group and *ortho* oxidation with IBX gave the unstable orthoquinone **68** through decarboxylation. Finally, treatment with HF gave kendomycin (**19**). This completed a second-generation synthesis with an improved overall yield (0.74%) compared to the previous version (0.026%).



Scheme 9 Nakata's total synthesis of kendomycin (**19**)

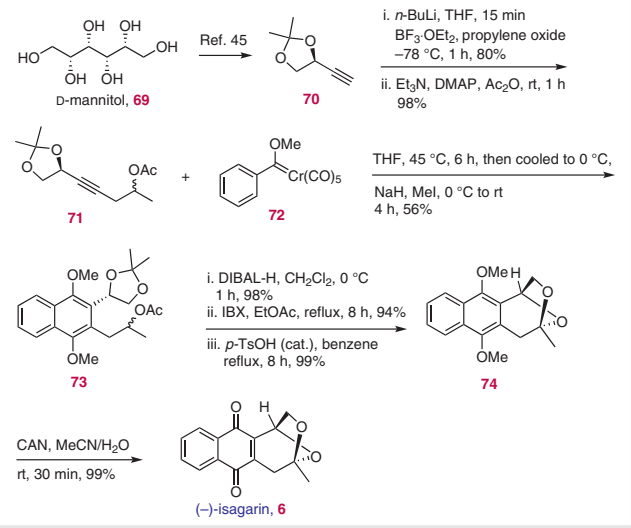


Scheme 10 Nakata's second-generation total synthesis of kendomycin (**19**)

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

3.6 Stereoselective Synthesis of the Tetracyclic Naphthoquinone, (–)-Isagarin (6)[43]

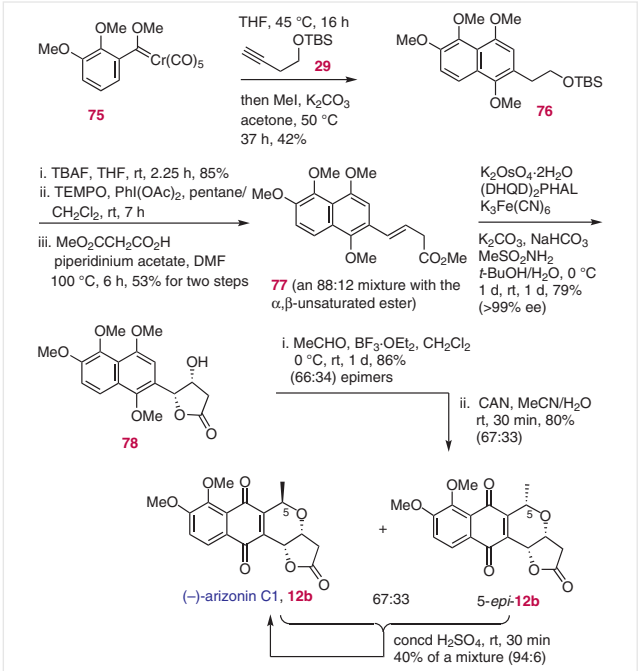
Isagarin, a new type of tetracyclic naphthoquinone, was isolated by Van Puyvelde and co-workers from the roots of *Pentas longiflora* Oliv. (Rubiaceae),[44a] which possess a broad range of medicinal properties.[44b–d] A concise synthesis of (–)-isagarin by our group is depicted in Scheme 11.[43] The alkyne **70** was prepared from D-mannitol (**69**) as reported in the literature.[45] Addition of **70** to propylene oxide and acetylation resulted in the acetate **71**. The Dötz benzannulation with carbene **72** and in situ methylation then gave naphthalene **73** in 56% yield. The in situ methylation helped to avoid the formation of regioisomers. Further, the sequence of acetate reduction, hydroxy oxidation and transketalization provided **74** in 91% yield (three steps) from **73**. Finally, quinone formation produced (1*S*,4*R*)-(–)-isagarin (**6**) in 99% yield.



Scheme 11 Synthesis of (–)-isagarin (**6**)

3.7 Total Synthesis of (+)- and (–)-Arizonins B1 (12a) and C1 (12b)[46]

Brückner and co-workers reported a concise synthesis of arizonin C1 (**12b**) (Scheme 12),[46a] a member of six anti-Gram-positive antibiotics isolated from *Actinoplanes arizonaensis* sp. nov., strain AB660D-122, by Hochlowski et al.[47] The Dötz benzannulation of Fischer carbene **75** with alkyne **29** furnished the naphthol that was methylated in the same-pot to give **76** in 42% yield. The latter, on TBS removal, hydroxyl oxidation and olefination under modified Knoevenagel condensation,[24] furnished the β,γ-unsaturated ester **77** (as an 88:12 mixture with the α,β-regioisomer). Asymmetric dihydroxylation then gave the lactone **78** in 79% yield and >99% ee. The oxa-Pictet–Spengler reaction with acetaldehyde furnished a mixture of C5-epimers in 86% yield and in a 66:34 ratio. Subsequent CAN oxidation afforded a mixture of **12b** and 5-*epi*-**12b** in a 67:33 ratio and 80% yield. The epimer ratio of this mixture increased to 94:6 toward arizonin C1 (**12b**) on treatment with concentrated H_2SO_4.

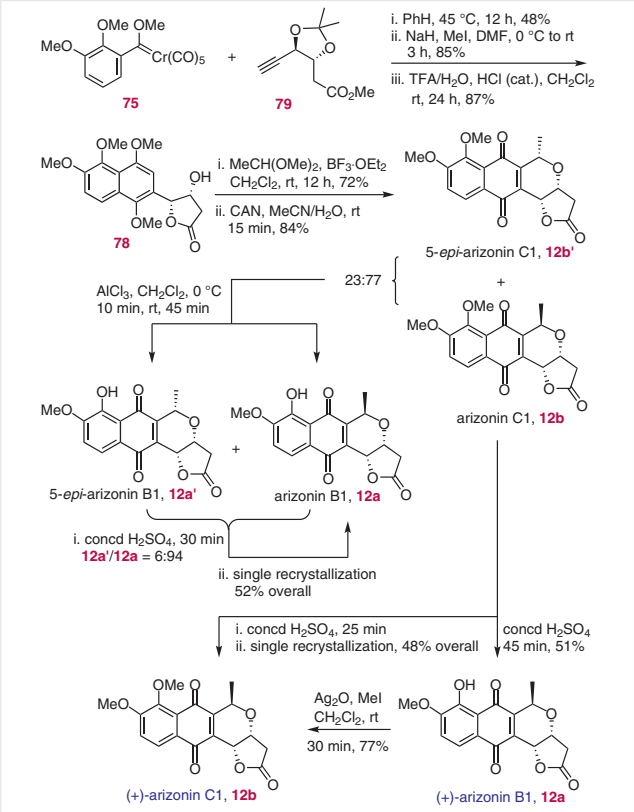


Scheme 12 Total synthesis of (–)-arizonin C1 (**12b**) by Brückner and co-workers

We also achieved an efficient total synthesis of arizonins B1 (**12a**) and C1 (**12b**) by employing functionalized alkyne substrate **79** (Scheme 13).[46b] The Dötz benzannulation of carbene **75** with alkyne **79** gave the corresponding naphthol (48%), which was methylated (85%) and then subjected to acid-mediated cyclization to give the lactone **78** in 87% yield. Subsequent oxa-Pictet–Spengler reaction and CAN oxidation furnished **12b′** and arizonin C1 (**12b**) in a 23:77 ratio. The $AlCl_3$-mediated demethylation of the mixture gave the expected quinone mixture in 80% yield. Treatment of this mixture with concentrated H_2SO_4 resulted in C-5 epimerization giving **12a′**/**12a** in a 6:94 ratio and a single recrystallization gave arizonin B1 (**12a**) in 52% yield from the mixture. On the other hand, stirring the mixture of **12b′**/**12b** with concentrated H_2SO_4 provided directly arizonin B1 (**12a**) in 51% yield via a remarkable regioselective C-7 demethylation and C-5 epimerization. Ag_2O/MeI-based methylation of **12a** gave arizonin C1 (**12b**) in 77% yield. Alternatively, treatment with concentrated H_2SO_4 over a shorter time of 25 min gave only the C-5 epimerized product (**12b′**/**12b** = 6:94 ratio). A single recrystallization then gave arizonin C1 (**12b**) in 48% yield. This work described the first asymmetric synthesis of arizonin B1.

© 2020. Thieme. All rights reserved.

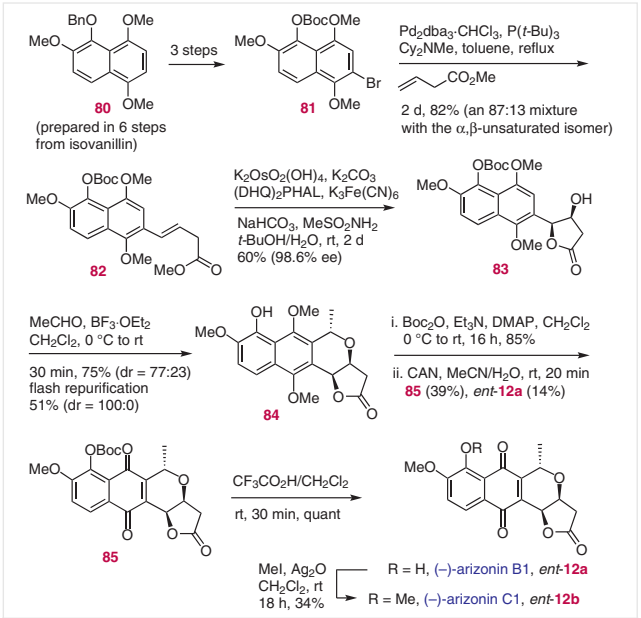
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



Scheme 13 Our syntheses of (+)-arizonin B1 (**12a**) and (+)-arizonin C1 (**12b**)

In our work on the synthesis of (+)-arizonins B1 and C1, we observed discrepancies in the signs of the optical rotations for both molecules compared to that reported for the natural isolate and that by Brückner.[46a] We also synthesized the enantiomer of arizonin C1, i.e., *ent*-**12b**, by following the literature method and found it to have the same value[46b] as the natural isolate and Brückner's compound. Although at that stage we could not resolve these differences, a subsequent paper by Brückner and co-workers[46c] indicated that our report was correct and that probably their samples corresponding to lactone **78** had been exchanged between the two enantiomers.

Brückner's alternative syntheses of (–)-arizonin B1 and (–)-arizonin C1 are depicted in Scheme 14. The required substituted naphthalene **80** was prepared from isovanillin in six steps and a further 3 steps were required to arrive at bromo derivative **81**. The latter on Heck coupling with methyl 3-butenoate gave **82** in 82% yield, containing 13% of the α,β-unsaturated ester isomer. Asymmetric dihydroxylation gave the lactone **83** (60%, 98.6% ee), which on oxa-Pictet–Spengler reaction provided the *trans*-pyran compound **84** (dr = 77:23) that was purified by flash chromatography to give the pure diastereomer. The Boc group was cleaved during this reaction and the free phenol compound **84** was found to decompose during the CAN oxidation for quinone formation. Hence Boc reprotection was executed followed by CAN oxidation to produce **85**. TFA-mediated Boc removal then gave (–)-arizonin B1 (*ent*-**12a**). The latter was methylated to give (–)-arizonin C1 (*ent*-**12b**). The obtained optical rotations were in agreement with respect to the sign as obtained by us (Scheme 13),[46b] and thereby confirming that their earlier synthesis (Scheme 12) had sample of **78** that was actually of its enantiomer.

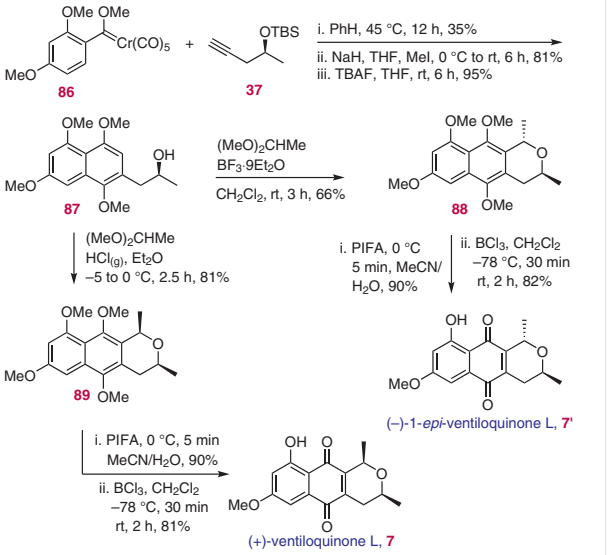


Scheme 14 Brückner's alternative syntheses of (–)-arizonin B1 and (–)-arizonin C1 and confirmation of the correctness of the chemistry reported by our group in Scheme 13

3.8 Synthesis of (+)-Ventiloquinone L (7) and (–)-1-*epi*-Ventiloquinone L (7′)[48]

Ventiloquinone L (**7**), with a *syn*-configured 1,3-dimethypyran, was isolated from the root bark of *Ventilago goughii*[49a] and shown to inhibit specific topoisomerase II.[49b] In 2012, we completed a short synthesis of **7** (Scheme 15).[48] Reaction of Fischer carbene **86** with alkyne **37** gave the benzannulated product, which on methylation and TBS removal afforded the alcohol **87**. Similar to our previous work on cardinalin-3, treatment of **87** under normal oxa-Pictet–Spengler conditions gave the *anti*-1,3-dimethylpyran product **88** in a 72:28 diastereomer ratio. On the other hand, the reaction of **87** with $(MeO)_2CHMe$ under dry HCl gas bubbling gave the *syn*-1,3-dimethylpyran product **89** with a dr of 88:12. The separated diastereomer **89** on quinone formation under phenyliodine bis(trifluoroacetate) (PIFA) conditions and regioselective demethylation with BCl_3 gave (+)-ventiloquinone L (**7**) in 73% yield from **89**. Similarly, quinone formation and demethylation using **88** furnished (–)-1-*epi*-ventiloquinone L (**7′**) in identical yield.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

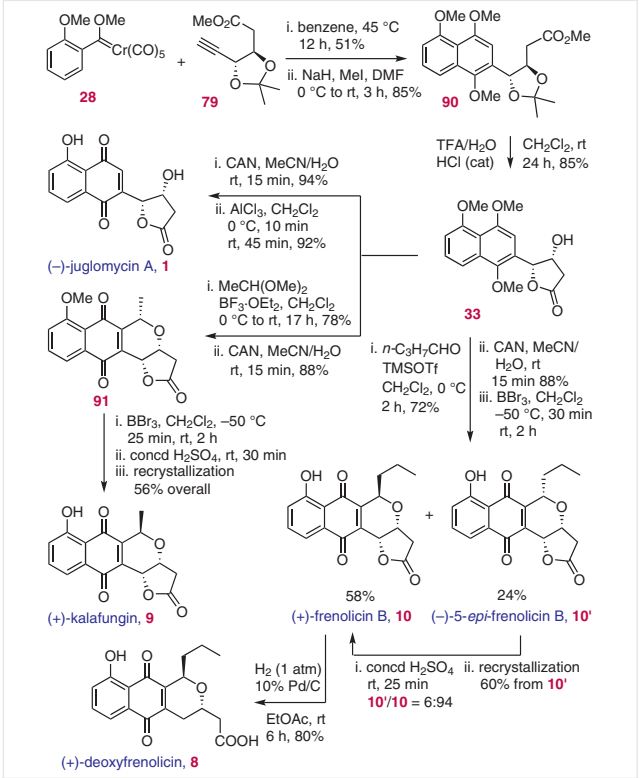


Scheme 15 Synthesis of (–)-1-*epi*-ventiloquinone L (**7**) and (+)-ventiloquinone L (**7′**)

3.9 Synthesis of (–)-Juglomycin A (1), (+)-Deoxyfrenolicin (8), (+)-Kalafungin (9) and (+)-Frenolicin B (10)[50]

Our group again utilized the potential of the Dötz benzannulation reaction for the simple and efficient chiral-pool-based synthesis of (–)-juglomycin A (**1**),[21] (+)-kalafungin (**9**), (+)-frenolicin B (**10**) and (+)-deoxyfrenolicin (**8**) (Scheme 16).[50] Kalafungin was first isolated by Bergy[51] from *Streptomyces tanashiensis*, while frenolicin B and deoxyfrenolicin were isolated by Omura and co-workers[52] from the fermentation of *Streptomyces roseofulvus*, strain No. AM-3867. The synthesis commenced with the Dötz benzannulation reaction of **28** with the alkyne **79** (prepared in six steps from D-glucono-δ-lactone) to give the naphthol, which on methylation produced **90**. Acetonide deprotection and lactonization then afforded the lactone **33** in 85% yield. Oxidation of **33** with CAN and $AlCl_3$-mediated demethylation gave (–)-juglomycin A (**1**). The lactone **33** on oxa-Pictet–Spengler reaction (to the *syn*-pyran diastereomer only) and CAN oxidation resulted in C-5 *epi*-methylkalafungin (**91**). Our earlier described protocol of demethylation with BBr_3 also induced C-5 isomerization, which was increased further by H_2SO_4 treatment and a final recrystallization afforded (+)-kalafungin (**9**) in 56% overall yield from **91**.

Similarly, the oxa-Pictet–Spengler reaction of **33** with butyraldehyde using the Lewis acid TMSOTf followed by CAN oxidation gave a mixture of diastereomers with the *syn*-isomer as the major product. This mixture on BBr_3-based demethylation also underwent C-5 epimerization resulting in the *anti*-diastereomer **10** as the major product. These diastereomers were separated in 58% and 24% yields, respectively, resulting in (+)-frenolicin B (**10**) and 5-*epi*-frenolicin B (**10′**). The latter minor diastereomer was isomerized by H_2SO_4 treatment and recrystallized to give (+)-frenolicin B (**10**) in 60% yield. Hydrogenation of **10** resulted in lactone opening giving (+)-deoxyfrenolicin (**8**) in 80% yield.

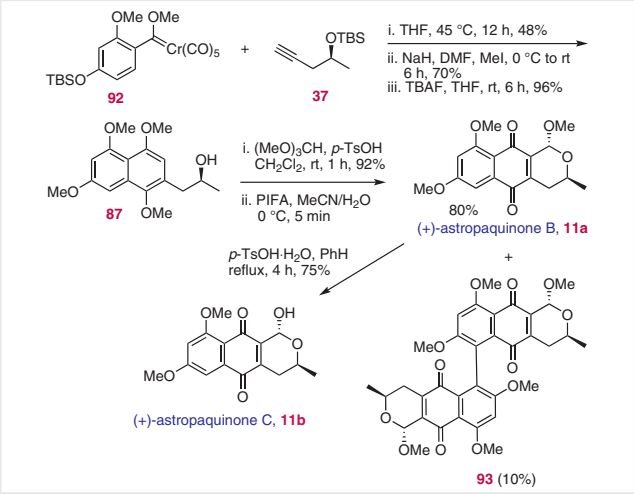


Scheme 16 Synthesis of (–)-juglomycin A (**1**), (+)-kalafungin (**9**), (+)-frenolicin B (**10**) and (+)-deoxyfrenolicin (**8**)

3.10 Synthesis of (+)-Astropaquinone B (11a) and (+)-Astropaquinone C (11b)[53]

Astropaquinones B and C were isolated by Wang and co-workers from the cultures of the freshwater fungus *Astrosphaeriella papuana* YMF 1.01181, and were found to demonstrate moderate antagonistic activity against fungi and bacteria.[54] Since in our previous synthesis of ventiloquinone L (**7**) (Scheme 15), the Dötz benzannulation using Fischer carbene **86** gave a lower yield of 35%, we considered the use of the different Fischer carbene **92** (Scheme 17) for the synthesis of the astropaquinones. The carbene **92** on reaction with alkyne **37** gave the naphthol product in 48% yield. This on methylation and TBS removal furnished the alcohol **87**. Subsequent oxa-Pictet–Spengler reaction of **87** with $(MeO)_3CH$ and PIFA-based oxidation gave the *anti*-pyran acetal (+)-astropaquinone B (**11a**) in 80% yield. During PIFA oxidation the dimerized compound **93** was isolated in 10% yield. Partial acetal hydrolysis of compound **11a** gave (+)-astropaquinone C (**11b**) in 75% yield.

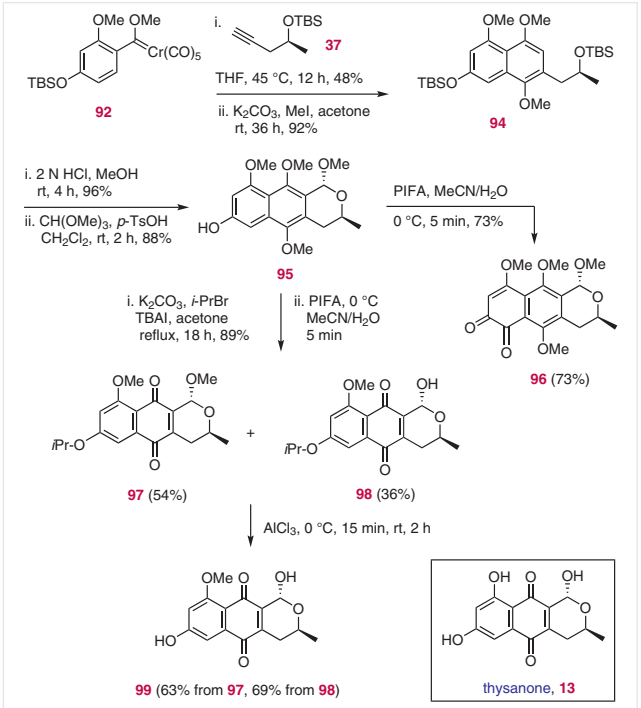
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



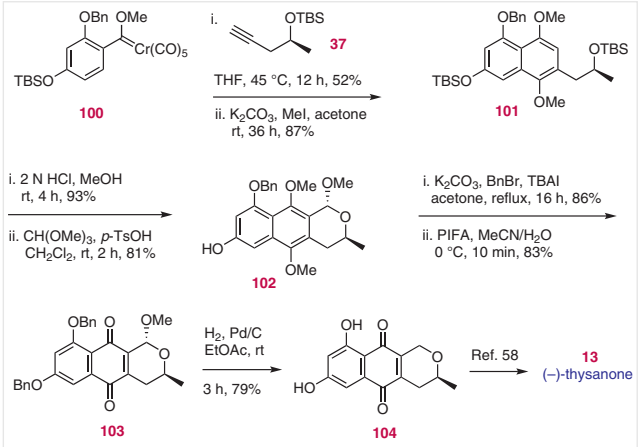
Scheme 17 Synthesis of (+)-astropaquinone B (**11a**) and (+)-astropaquinone C (**11b**)

3.11 Synthesis of (–)-Thysanone (13)[55]

(–)-Thysanone (**13**), a pyranonaphthoquinone antibiotic, was isolated from the solid-state fermentation of the fungus *Thysanophora penicilloides* (MF 5636, Merck Culture Collection)[56] and shows inhibition against human rhinoviruses (HRVs) 3C-protease (IC_{50} = 13 μg/mL), which are responsible for afflictions such as polio, hepatitis A and foot and mouth diseases.[57] We considered a concise synthesis of compound **13** as shown in Scheme 18.[55] The Dötz benzannulation of **92** with the alkyne **37** gave the corresponding naphthol, which on methylation provided compound **94**. TBS deprotection and oxa-Pictet–Spengler reaction with $CH(OMe)_3$ then gave the *trans*-acetal **95** in 84% yield over two steps. Subsequent PIFA-mediated quinone formation unfortunately gave the *ortho*-quinone **96** in 73% yield. Hence protection of the phenol as an *iso*-propyl ether and quinone formation resulted in a mixture of **97** and the hemiacetal **98** in 54% and 36% yields, respectively. Subsequent dealkylation of **97** or **98** with $AlCl_3$ gave *O*-methylthysanone (**99**) without demethylation. Other dealkylating agents (BBr_3, BCl_3 or $TiCl_4$) also gave similar results. In our ventiloquinone L synthesis, the C9-OMe group was demethylated quite selectively in the presence of the C7-OMe group using BCl_3.[48] Hence an alternative strategy using different protecting groups was considered (Scheme 19). The Fischer carbene **100**, prepared in four steps, on Dötz benzannulation with the alkyne **37** gave the expected naphthol, which on subsequent methylation provided compound **101**. This on TBS deprotection and oxa-Pictet–Spengler reaction with $CH(OMe)_3$ gave the *trans*-acetal **102** in 75% yield over two steps. Benzyl protection of the phenol in **102** (86%) and quinone formation provided the quinone **103** in 83% yield. Debenzylation of the latter under hydrogenolysis conditions unfortunately also reduced the acetal giving the pyran **104** in 79% yield. The two-step conversion of **104** into thysanone is known in the literature[58] and thus our route constitutes a formal synthesis of thysanone (**13**).



Scheme 18 Fernandes' synthesis of *O*-methylthysanone (**99**)



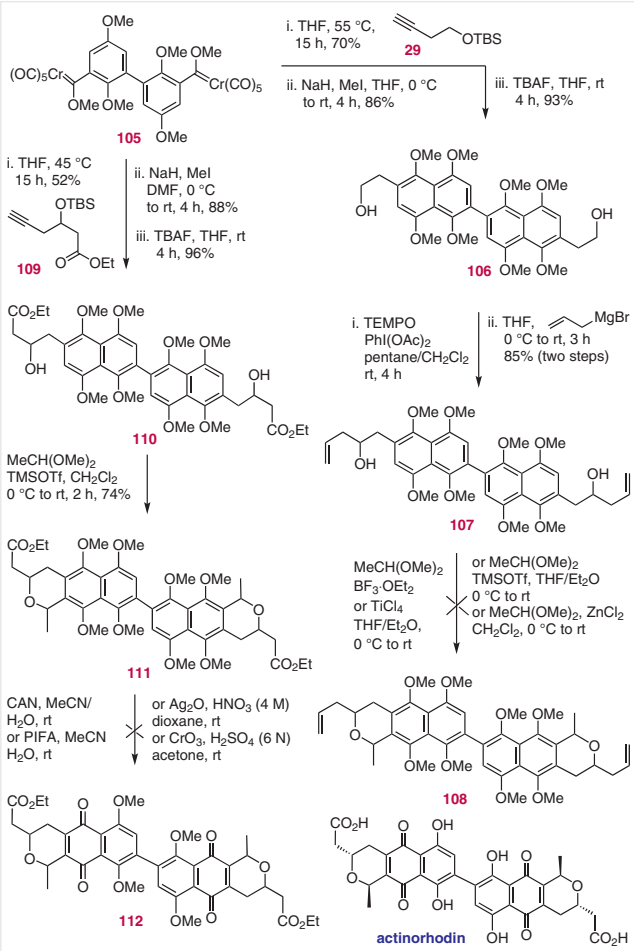
Scheme 19 Fernandes' formal synthesis of (–)-thysanone (**13**)

3.12 Synthetic Studies on γ-Actinorhodin, Actinorhodin and Crisamicin A[4,59]

Actinorhodin and γ-actinorhodin are interesting dimeric pyranonaphthoquinones isolated from *Streptomyces coelicolor*[60] (soil-dwelling bacteria) with promising bioactivity against *Staphylococcus aureus* bacteria[60b] located in the human respiratory tract and on the skin. Crisamicin A,

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

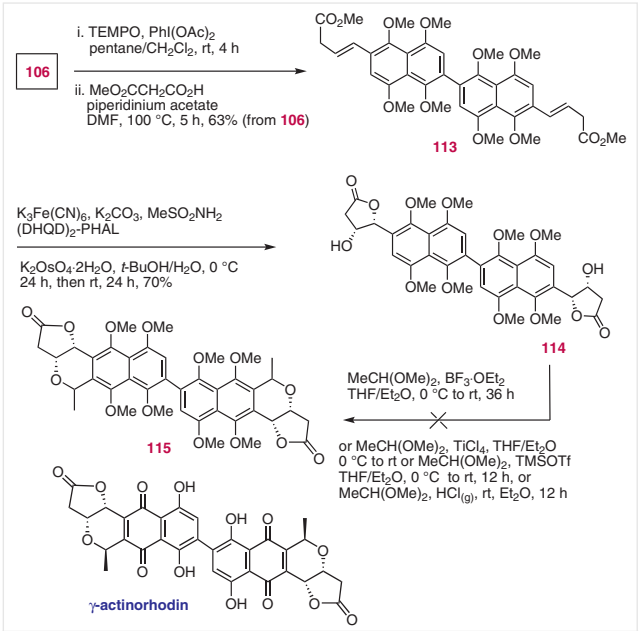
isolated from *Micromonospora purpureochromogenes*,[61] shows activity against B16 murine melanoma cells and the herpes simplex and vesicular stomatitis viruses.[62] A promising bidirectional Dötz benzannulation approach was attempted toward the syntheses of these compounds (Scheme 20).



Scheme 20 Synthetic studies on actinorhodin

Reaction of the dimeric Fischer carbene **105** with alkyne **29** gave the expected naphthol (70%) and subsequent methylation and TBS removal provided the dimeric alcohol **106** (86%). The latter on alcohol oxidation to the aldehyde followed by an allyl Grignard reaction gave **107**. All attempts to construct the pyran ring by an oxa-Pictet–Spengler reaction failed to give the pyran **108**. When the reaction was attempted on a monomeric compound, participation of the homoallylic double bond in a Prins-type reaction was observed. Alternatively, the Dötz benzannulation of **105** with alkyne **109** gave the corresponding naphthol (52%) and subsequent methylation and TBS deprotection provided the dimeric alcohol **110**. The latter was subjected to an oxa-Pictet–Spengler reaction to give a *syn*/*anti* mixture of pyran **111**. This on CAN oxidation gave a complex mixture. Other conditions using Ag_2O, PIFA and CrO_3 resulted in either decomposition or delivered regioisomeric and differently oxidized quinone mixtures arising from multiple 1,4-dimethoxy aryl units and/or possible quinone isomerizations.

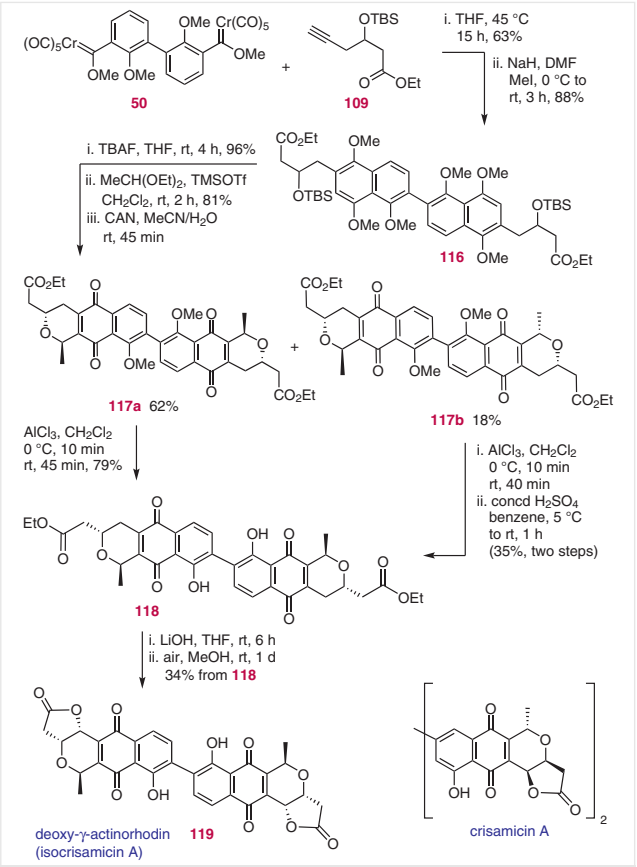
Alternatively, the decarboxylative–deconjugative Knoevenagel reaction on the aldehyde derived from **106** gave the ester **113** (Scheme 21). This on asymmetric dihydroxylation furnished the bis-lactone **114**. The latter resisted the oxa-Pictet–Spengler reaction to install the pyran ring of **115**. Similar reactions were quite successful on monomeric molecules in the arizonin synthesis.[46] Hence the failure was attributed to the electron density on the naphthyl rings having four methoxy groups on each ring.



Scheme 21 Synthetic studies on γ-actinorhodin

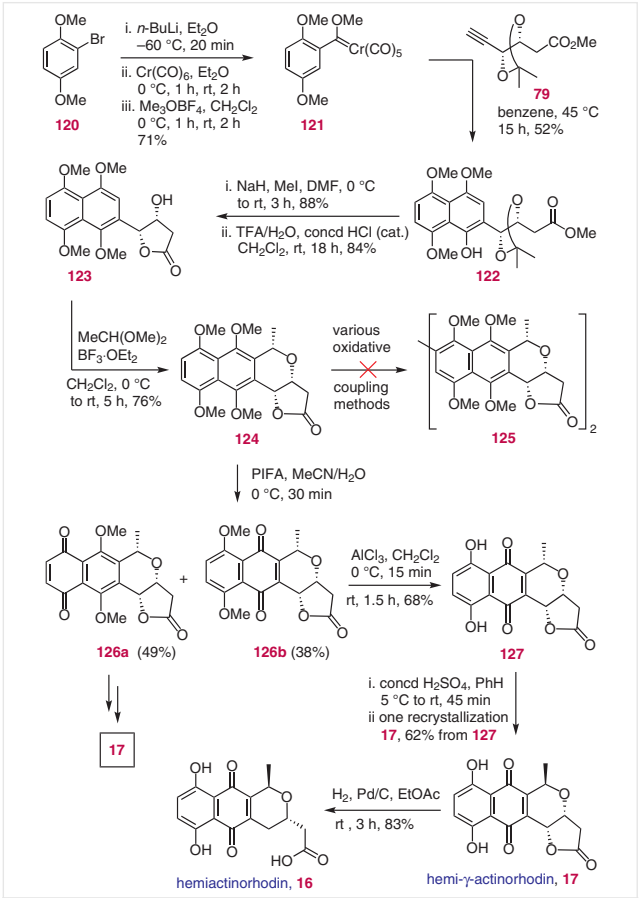
In another approach, we considered the synthesis of deoxy-γ-actinorhodin (Scheme 22).[4] The Dötz benzannulation of **50** with alkyne **109** gave the expected naphthol, which on methylation provided **116**. Removal of the TBS group followed by an oxa-Pictet–Spengler reaction gave a *syn*/*anti*-pyran mixture that was oxidized successfully to the quinone mixture. Separation of the latter furnished the *anti*/*anti*-pyran **117a** and the *anti*/*syn*-pyran **117b** in 62% and 18% yields, respectively. Demethylation of **117a** to **118** (79%) and subsequent ester hydrolysis and air oxidation resulted in cyclization, possibly through the quinone methide intermediate, to furnish deoxy-γ-actinorhodin (isocrisamicin A) (**119**). The undesired isomer **117b** on demethylation was subjected to concentrated H_2SO_4 treatment for benzylic epimerization giving **118** with 35% recovery.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



Scheme 22 Synthetic studies on γ-actinorhodin, actinorhodin and crisamicin A

Considering the possible oxidative homocoupling of monomeric units to the dimeric molecules actinorhodin and γ-actinorhodin, we planned to synthesize the former monomers (Scheme 23).[59] Dötz benzannulation of the Fischer carbene **121** (prepared from **120**) with alkyne **79** gave the naphthol **122** in 52% yield. Conversion of the phenol group into a methyl ether and lactonization provided **123** (74% over two steps). A subsequent oxa-Pictet–Spengler reaction gave the *syn*-pyran **124** in 76% yield. Various oxidative coupling methods using DDQ,[63a] $FeCl_3$,[63b,c] CAN,[63d] PIFA and Ag_2O[63e] failed to dimerize the monomer **124**. Under CAN or PIFA conditions, a mixture of quinone regioisomers **126a** and **126b** was obtained (49% and 38% yields, respectively, with PIFA). The separated quinone **126b** on demethylation to **127** (68%) and isomerization mediated by concentrated H_2SO_4 gave the *trans*-epimer in a 93:7 ratio. A single recrystallization furnished hemi-γ-actinorhodin (**17**) in 62% yield from **127**. Benzylic hydrogenation then opened the lactone to give hemiactinorhodin (**16**) in 83% yield. The undesired terminal quinone on BBr_3-mediated demethylation also underwent quinone isomerization and C-5 epimerization to give a mixture of **17** and **127** in a 62:38 ratio and 45% yield. The obtained *syn*-isomer was epimerized fully by H_2SO_4 treatment and recrystallization to give hemi-γ-actinorhodin (**17**).



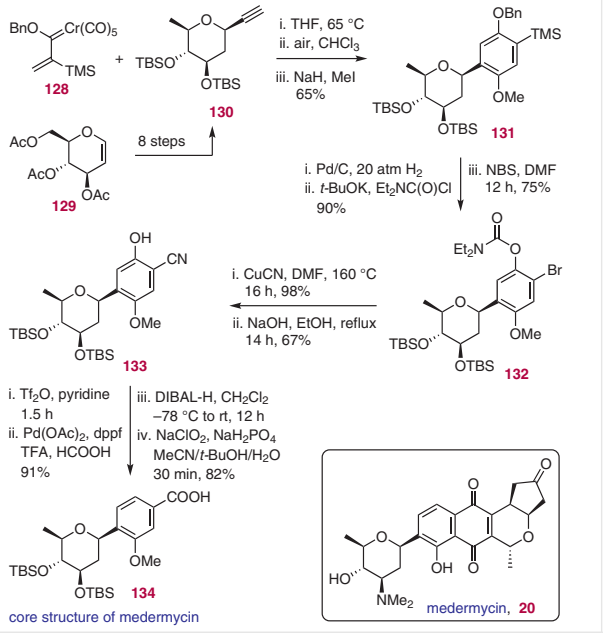
Scheme 23 Fernandes' synthesis of hemi-γ-actinorhodin (**17**) and hemiactinorhodin (**16**)

3.13 Synthesis of the Core Structure of Medermycin (20)[64]

Medermycin was first isolated in 1976 by Takano et al.[65a] from *Streptomyces* sp. and has a unique β-*C*-glycoside linkage of an aminosugar, D-angolosamine. It shows prominent activity against Gram-positive bacteria and also inhibits human leukemic K-562 cells and platelet aggregation.[65b] Hong and co-workers[64] developed a Dötz benzannulation based strategy for the preparation of the *C*-arylglycoside moiety of medermycin (Scheme 24). The glycoside-based alkyne **130** was prepared from 3,4,6-*O*-acetyl D-glucal (**129**) in eight synthetic steps. The reaction of the latter with the Fischer carbene **128** gave the corresponding phenol that was methylated to afford the *C*-arylglycoside **131** in 65% yield. Subsequent benzyl deprotection, *O*-carbamate formation and aryl bromination gave the intermediate **132**. Displacement of Br with CN and carbamate hydrolysis provided the phenol **133**. Next, phenol deoxygenation via the triflate

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

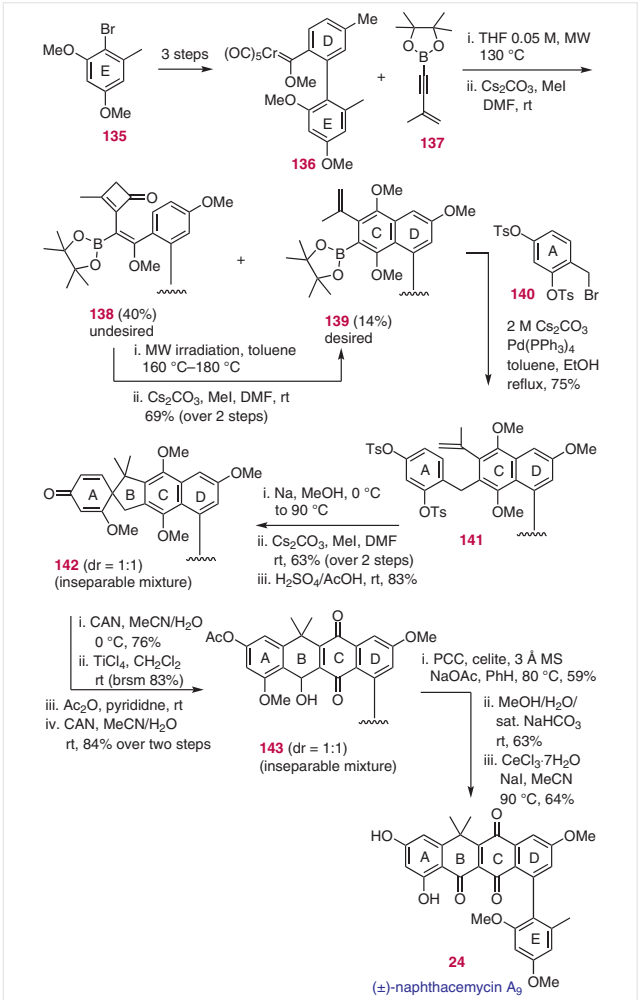
followed by DIBAL-H reduction of the nitrile to an aldehyde and oxidation gave the acid **134**, which represents the core structure of medermycin (**20**).



Scheme 24 Hong's synthesis of the medermycin core structure

3.14 Total Synthesis of (±)-Naphthacemycin A_9 (24)[66]

Naphthacemycin A_9 (**24**) is a member of a series of new antibiotics isolated by Ōmura et al. from the culture broth of *Streptomyces* sp. KB-3346-5.[67] This compound demonstrated anti-MRSA activity and could be used to treat bacteria showing β-lactam resistance. Compound **24** contains a naphthacene structure with the E-ring having atropchirality. The total synthesis of (±)-naphthacemycin A_9 (**24**) by Ōmura et al. is depicted in Scheme 25.[66] The Fischer carbene **136** was prepared in three steps from **135** and then reacted with the alkyne **137** under microwave irradiation to give the phenol, which on methylation provided **139** as the minor product. The major product was the cyclobutenone **138**. Following the report of Moore and Perri,[68] compound **138** was thermally rearranged into the intermediate ketene that then cyclized to give the phenol, which on methylation furnished **139**. The subsequent Suzuki–Miyaura coupling of the latter with bromide **140** provided compound **141**. Removal of both Ts groups, methylation and acid-mediated Friedel–Crafts cyclization led to the spirocyclic dienone **142** as an inseparable 1:1 mixture of diastereomers. Next, CAN-mediated *p*-quinone formation, $TiCl_4$-based dienone–phenol rearrangement, acetylation of the phenol and benzylic oxidation with CAN gave the alcohol **143** as an inseparable diastereomer mixture. Alcohol oxidation to the ketone and deacetylation gave the methyl-naphthacemycin that resisted demethylation by boron trihalides. However, demethylation was achieved by reaction with $CeCl_3{\cdot}7H_2O$ and NaI to furnish the target molecule (±)-naphthacemycin A_9 (**24**) in 64% yield.



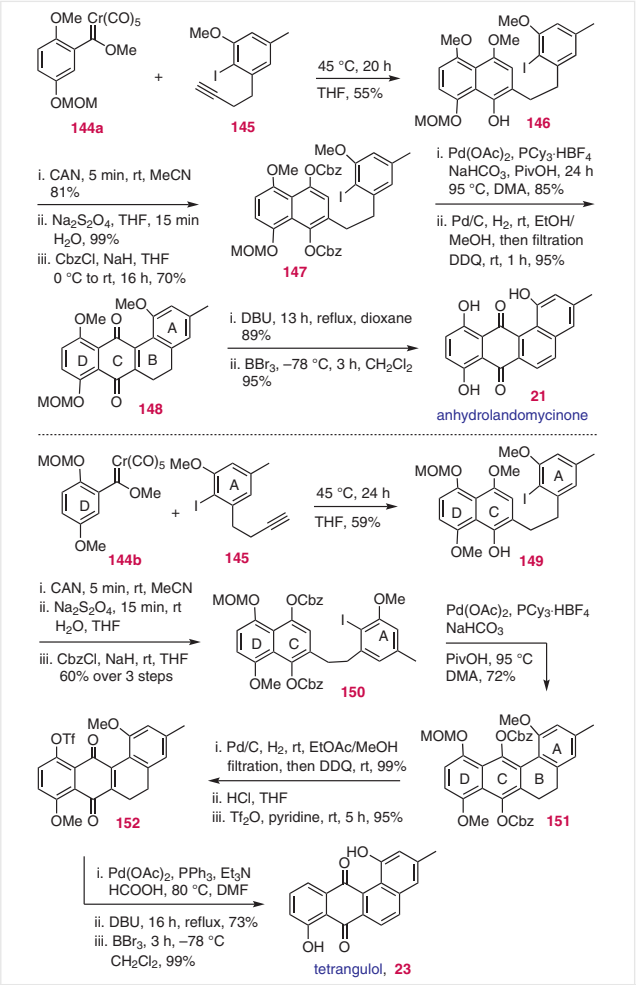
Scheme 25 Ōmura's synthesis of (±)-naphthacemycin A_9 (**24**)

3.15 Total syntheses of Anhydrolandomycinone (21), Landomycinone (22) and Tetrangulol (23)[69]

Landomycins, with potent antiproliferation and antibiotic activities,[70] consist of an angular tetracyclic unit fused with a deoxyoligosaccharide framework and were isolated from *Streptomyces* bacteria.[71] Mong et al.[69] have synthesized anhydrolandomycinone (**21**), tetrangulol (**23**) and landomycinone (**22**) using the Dötz benzannulation and C–H activation (Schemes 26 and 27). The reaction of Fischer carbene **144a** with alkyne **145** afforded the naphthol **146** in 55% yield. This was then subjected to CAN oxidation, hydroquinone formation and CBz protection to give **147**. Subsequent Pd-catalyzed C–H-activation-based intramolecular cyclization, CBz removal and quinone formation led to **148**. The latter on aromatization, demethylation and MOM

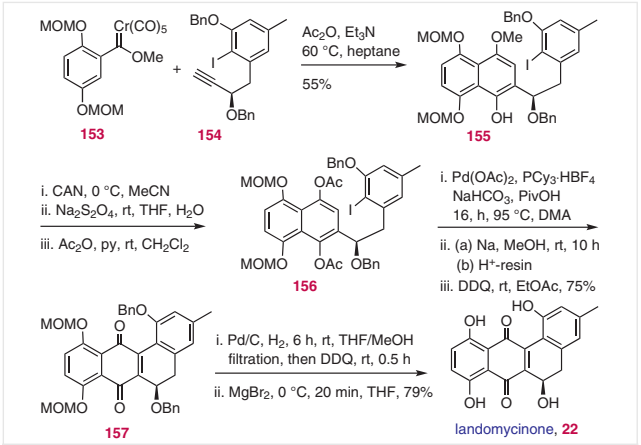
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

group removal gave anhydrolandomycinone (**21**). Similarly, toward the synthesis of tetrangulol, the Dötz benzannulation of Fischer carbene **144b** (a regioisomer of **144a**) with alkyne **145** gave the naphthol **149** that on CAN oxidation, quinone reduction and CBz protection afforded **150**. The latter on C–H-activation-based cyclization gave **151**. Subsequent CBz removal, quinone formation, MOM deprotection and conversion of the phenol into OTf gave **152**. Finally, deoxygenation of the triflate, aromatization and demethylation furnished tetrangulol (**23**).



Scheme 26 Mong's total synthesis of anhydrolandomycinone (**21**) and tetrangulol (**23**)

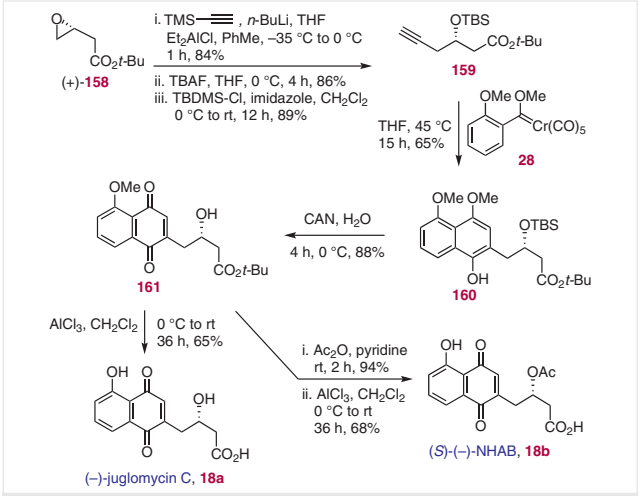
The synthesis of landomycinone (**22**) is shown in Scheme 27. The benzannulation of carbenes **153** with alkyne **154** gave the naphthol **155**, which on quinone formation, reduction and acetylation afforded the diacetate **156**. Subsequent intramolecular cyclization, acetate hydrolysis and careful quinone formation (no aromatization of the B ring) led to compound **157**. Finally, benzyl group removal under hydrogenolysis conditions and MOM deprotection gave landomycinone (**22**).



Scheme 27 Mong's total synthesis of landomycinone (**22**)

3.16 Synthesis of (–)-Juglomycin C (18a) and (–)-NHAB (18b)[72]

We recently completed step-economic and efficient syntheses of (*S*)-(–)-juglomycin C (**18a**) and (*S*)-(–)-NHAB (**18b**) employing the Dötz benzannulation reaction (Scheme 28).[72] The former was isolated from *Streptomyces* sp. 815 and 3094,[73a] while the latter is a shunt product from disruption of the *act*-VI-ORFA gene in *Streptomyces coelicolor* A3(2), which produces actinorhodin biosynthetically.[73b–d] In our synthesis, the chiral alkyne **159** was prepared from epoxide (±)-**158** by first resolving the racemic epoxide to obtain (+)-**158** in high enantiomeric excess (99% ee). Opening of the epoxide with TMS-acetylene, TMS removal and OTBS ether formation gave alkyne **159** in 64% overall yield from **158**. The subsequent Dötz benzannulation of Fischer carbene **28** with alkyne **159** gave the naphthol **160**. CAN-mediated quinone formation also caused TBS group removal giving



Scheme 28 Fernandes' syntheses of (–)-juglomycin C (**18a**) and (–)-NHAB (**18b**)

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

161 (88%) and demethylation with $AlCl_3$ also effected *t*-Bu group removal providing (–)-juglomycin C (**18a**) in a step-economic and convergent deprotection sequence. The acetylation of **161** and demethylation with concomitant *t*-Bu group removal gave (*S*)-(–)-NHAB (**18b**).

4 Conclusion

The Dötz benzannulation of Fischer carbenes has been increasingly used in the synthesis of natural products over the last decade. The reaction holds promise for the rapid generation of phenol or naphthol moieties possessing suitably placed substituents, whilst showing excellent control of the regioselectivity. The intramolecular version of tethering the Fisher carbene through an ether linkage and generation of a phenol and a macrocycle simultaneously holds potential for the future development of many related ansa-compounds. With the basic understanding of the reaction mechanism, the formation of other products can be minimized with careful control of the solvent, the temperature and the concentration. We strongly believe that this timely review abstracting the strategic use of the Dötz benzannulation/reaction in the synthesis of various natural products over the last decade will help in the future design and development of this reaction with a focus on natural products synthesis.

Funding Information

Generous funding by the Department of Science & Technology, Science and Engineering Research Board (DST-SERB), New Delhi (Grant Nos. EMR/2017/000499 and SB/S1/OC-42/2013) is gratefully acknowledged. A.K. and R.S.P. thank the Indian Institute of Technology Bombay (IIT Bombay) for a senior research fellowship and a postdoctoral research fellowship, respectively.

References

(1) Baran, P. S. *J. Am. Chem. Soc.* **2018**, *140*, 4751; and references cited therein.
(2) (a) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022. (b) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141. (c) Peterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451. (d) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329. (e) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461. (f) Thomford, N. E.; Senthebane, D. A.; Rowe, A.; Munro, D.; Seele, P.; Maroyi, A.; Dzobo, K. *Int. J. Mol. Sci.* **2018**, *19*, 1578.
(3) (a) Nematollahi, A.; Aminimoghadamfarouj, N.; Wiart, C. *J. Asian Nat. Prod. Res.* **2012**, *14*, 80. (b) Johann, L.; Belorgey, D.; Huang, H.-H.; Day, L.; Chessé, M.; Becker, K.; Williams, D. L.; Davioud-Charvet, E. *FEBS J.* **2015**, *282*, 3199. (c) Qiu, H.-Y.; Wang, P.-F.; Lin, H.-Y.; Tang, C.-Y.; Zhu, H.-L.; Yang, Y.-H. *Chem. Biol. Drug Des.* **2018**, *91*, 681. (d) Pinto, A. V.; de Castro, S. L. *Molecules* **2009**, *14*, 4570. (e) Hou, Y.; Vasileva, E. A.; Carne, A.; McConnell, M.; Bekhit, A.; El-Din, A.; Mishchenko, N. P. *RSC Adv.* **2018**, *8*, 32637. (f) Wellington, K. W. *RSC Adv.* **2015**, *5*, 20309.
(4) Mulay, S. V.; Fernandes, R. A. *Chem. Eur. J.* **2015**, *21*, 4842.
(5) Brimble, M. A.; Hassan, N. P. S.; Naysmith, B. J.; Sperry, J. *J. Org. Chem.* **2014**, *79*, 7169.
(6) Thrash, T. P.; Welton, T. D.; Behar, V. *Tetrahedron Lett.* **2000**, *41*, 29.
(7) (a) Dötz, K. H. *Angew. Chem. Int. Ed.* **1975**, *14*, 644. (b) Dötz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689.
(8) (a) Dötz, K. H.; Erben, H.-G.; Harms, K. *J. Chem. Soc., Chem. Commun.* **1989**, 692. (b) Grotjahn, D. B.; Dötz, K. H. *Synlett* **1991**, 381.
(9) (a) Wulff, W. D.; Yang, D. C.; Murray, C. K. *Pure Appl. Chem.* **1988**, *60*, 137. (b) Waters, M. L.; Brandvold, T. A.; Isaacs, L.; Wulff, W. D.; Rheingold, A. L. *Organometallics* **1998**, *17*, 4298. (c) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187. (d) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 3964. (e) Barluenga, J. *Pure Appl. Chem.* **2002**, *74*, 1317. (f) Minatti, A.; Dötz, K. H. *Top. Organomet. Chem.* **2004**, *13*, 123. (g) Fernandes, R. A.; Mulay, S. V. *Synthesis* **2014**, 1836. (h) Barluenga, J.; Martínez, S. *ARKIVOC* **2006**, *(vii)*, 129. (i) Santamaría, J.; Aguilar, E. *Org. Chem. Front.* **2016**, *3*, 1561. (j) Song, W.; Blaszczyk, S. A.; Liu, J.; Wang, S.; Tang, W. *Org. Biomol. Chem.* **2017**, *15*, 7490.
(10) (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. (b) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263. (c) Hauser, F. M.; Rhee, R. P. *J. Am. Chem Soc.* **1979**, *101*, 1628. (d) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061. (e) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273. (f) Rathwell, K.; Brimble, M. A. *Synthesis* **2007**, 643. (g) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892. (h) Hassan, N. P. S.; Naysmith, B. J.; Sperry, J.; Brimble, M. A. *Tetrahedron* **2015**, *71*, 7137. (i) Kumar, T.; Mane, V.; Namboothiri, I. N. N. *Org. Lett.* **2017**, *19*, 4283.
(11) (a) Dötz, K. H.; Pruskil, I. *J. Organomet. Chem.* **1981**, *209*, C4. (b) Dötz, K. H.; Kuhn, W. *Angew. Chem. Int. Ed.* **1983**, *22*, 732. (c) Wulff, W. D.; Tang, P.-C. *J. Am. Chem. Soc.* **1984**, *106*, 434. (d) Wulff, W. D.; Tang, P.-C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (e) Dötz, K. H.; Popall, M. *Angew. Chem. Int. Ed.* **1987**, *26*, 1158. (f) Dötz, K. H.; Popall, M.; Müller, G. *J. Organomet. Chem.* **1987**, *334*, 57. (g) Wulff, W. D.; Xu, Y. C. *J. Am. Chem. Soc.* **1988**, *110*, 2312. (h) Su, J.; Wulff, W. D.; Ball, R. G. *J. Org. Chem.* **1998**, *63*, 8440. (i) Wulff, W. D.; Su, J.; Tang, P.-C.; Xu, Y. C. *Synthesis* **1999**, 415.
(12) (a) Gilbert, A. M.; Miller, R.; Wulff, W. D. *Tetrahedron* **1999**, *55*, 1607. (b) Miller, R. A.; Gilbert, A. M.; Xue, S.; Wulff, W. D. *Synthesis* **1999**, 80. (c) Liptak, V. P.; Wulff, W. D. *Tetrahedron* **2000**, *56*, 1022.
(13) Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839.
(14) (a) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850. (b) Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *10*, 1599.
(15) Bao, J.; Wulff, W. D.; Dragisich, V.; Wenglowsky, S.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7616.
(16) White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235.
(17) (a) Hafner, A.; Hegedus, L. S.; de Weck, G.; Hawkins, B.; Dötz, K. H. *J. Am. Chem. Soc.* **1988**, *110*, 8413. (b) Bao, J.; Wulff, W. D.; Fumo, M. J.; Grant, E. B.; Heller, D. P.; Whitcomb, M. C.; Yeung, S.-M. *J. Am. Chem. Soc.* **1996**, *118*, 2166. (c) Gleichmann, M. M.; Dötz, K. H.; Hess, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10551. (d) Barluenga, J.; Aznar, F.; Palomero, M. A.; Barluenga, S. *Org. Lett.* **1999**, *1*, 541.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(18) (a) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1990**, *55*, 1919. (b) Moser, W. H.; Sun, L.; Huffman, J. C. *Org. Lett.* **2001**, *3*, 3389.
(19) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P. *Organometallics* **1994**, *13*, 102.
(20) Fernandes, R. A.; Chavan, V. P. *Tetrahedron Lett.* **2008**, *49*, 3899.
(21) Fernandes, R. A.; Chavan, V. P. *Tetrahedron: Asymmetry* **2011**, *22*, 1312.
(22) Ushiyama, K.; Tanakya, N.; Ono, H.; Ogata, H. *J. Antibiot.* **1971**, *24*, 197.
(23) Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416.
(24) (a) Ragoussis, N. *Tetrahedron Lett.* **1987**, *28*, 93. (b) Yamanaka, H.; Yokoyama, M.; Sakamoto, T.; Shiraishi, T.; Sagi, M.; Mizugaki, M. *Heterocycles* **1983**, *20*, 1541.
(25) (a) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317. (b) Johnson, R. A.; Sharpless, K. B. *Asymmetric Catalysis in Organic Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, **1993**, 227. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (d) Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis, 2nd ed*; Ojima, I., Ed.; Wiley-VCH: New York, **2000**, 399.
(26) Fernandes, R. A.; Chavan, V. P.; Ingle, A. B. *Tetrahedron Lett.* **2008**, *49*, 6341.
(27) Fernandes, R. A.; Chavan, V. P.; Mulay, S. V. *Tetrahedron: Asymmetry* **2011**, *22*, 487.
(28) (a) Schmid, H.; Meijer, T. M.; Ebnöther, A. *Helv. Chim. Acta* **1950**, *33*, 595. (b) Schmid, H.; Ebnöther, A.; Meijer, T. M. *Helv. Chim. Acta* **1950**, *33*, 1751.
(29) Bianchi, C.; Ceriotti, G. *J. Pharm. Sci.* **1975**, *64*, 1305.
(30) (a) Chen, Z.; Huang, H.; Wang, C.; Li, Y.; Ding, J. *Zhongcaoyao* **1981**, *12*, 484. (b) Ding, J.; Huang, H. *Zhongcaoyao* **1982**, *13*, 499.
(31) Otani, T.; Sugimoto, Y.; Aoyagi, Y.; Igarashi, Y.; Furumai, T.; Saito, N.; Yamada, Y.; Asao, T.; Oki, T. *J. Antiobiot.* **2000**, *53*, 337.
(32) Tanada, Y.; Mori, K. *Eur. J. Org. Chem.* **2001**, 4313.
(33) Fernandes, R. A.; Mulay, S. V. *J. Org. Chem.* **2010**, *75*, 7029.
(34) Fernandes, R. A.; Chavan, V. P. *Eur. J. Org. Chem.* **2010**, 4306.
(35) Chen, Z.; Huang, H.; Wang, C.; Li, Y.; Ding, J.; Ushio, S.; Hiroshi, N.; Yoichi, I. *Chem. Pharm. Bull.* **1986**, *34*, 2743.
(36) Chen, Z.; Huang, H.; Wang, C.; Li, Y.; Ding, J. *Chin. Tradit. Herb. Drugs* **1981**, *12*, 483.
(37) Fernandes, R. A.; Mulay, S. V. *Synlett* **2010**, 2667.
(38) (a) Buchanan, M. S.; Gill, M.; Yu, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 919. (b) Buchanan, M. S.; Gill, M.; Yu, J. *Aust. J. Chem.* **1997**, *50*, 1081.
(39) (a) Tanaka, K.; Watanabe, M.; Ishibashi, K.; Matsuyama, H.; Saikawa, Y.; Nakata, M. *Org. Lett.* **2010**, *12*, 1700. (b) Tanaka, K.; Matsuyama, H.; Watanabe, M.; Fujimori, Y.; Ishibashi, K.; Ozawa, T.; Sato, T.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2014**, *79*, 9922.
(40) (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. JP Patent 08231551, **1996**; *Chem. Abstr.* **1996**, *125*, 326518. (b) Funahashi, Y.; Ishimaru, T.; Kawamura, N. JP Patent 08231552, **1996**; *Chem. Abstr.* **1997**, *126*, 6553. (c) Su, M. H.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. US Patent 5728727, **1998**; *Chem. Abstr.* **1998**, *128*, 239489. (d) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 323.
(41) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(42) Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331.
(43) Fernandes, R. A.; Ingle, A. B. *Eur. J. Org. Chem.* **2011**, 6624.
(44) (a) Van Puyvelde, L.; El Hady, S.; De Kimpe, N.; Feneau-Dupont, J.; Declercq, J.-P. *J. Nat. Prod.* **1998**, *61*, 1020. (b) Kokwora, J. O. *Medicinal Plants of East Africa*; East African Literature Bureau: Kampala/Nairobi/Dar es Salaam, **1976**, 190. (c) Heyndrickx, G.; Brioen, P.; Van Puyvelde, L. *J. Ethnopharmacol.* **1992**, *35*, 259. (d) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erkelens, C.; Verpoorte, R. *Magn. Reson. Chem.* **1993**, *31*, 329.
(45) (a) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447. (b) Pietruszka, J.; Witt, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4293.
(46) (a) Mahlau, M.; Fernandes, R. A.; Brückner, R. *Eur. J. Org. Chem.* **2011**, 4765. (b) Fernandes, R. A.; Mulay, S. V.; Chavan, V. P. *Tetrahedron: Asymmetry* **2013**, *24*, 1548. (c) Neumeyer, M.; Brückner, R. *Eur. J. Org. Chem.* **2017**, 2512.
(47) Hochlowski, J. E.; Brill, G. M.; Anders, W. W.; Spanton, S. G.; McAlpine, J. B. *J. Antibiot.* **1987**, *40*, 401.
(48) Fernandes, R. A.; Ingle, A. B.; Chavan, V. P. *Org. Biomol. Chem.* **2012**, *10*, 4462.
(49) (a) Jammula, S. R.; Pepalla, S. B.; Telikepalli, H.; Rao, K. V. J.; Thomson, R. H. *Phytochemistry* **1991**, *30*, 3741. (b) Sperry, J.; Lorenzo-Castrillejo, I.; Brimble, M. A.; Machín, F. *Bioorg. Med. Chem.* **2009**, *17*, 7131.
(50) Fernandes, R. A.; Chavan, V. P.; Mulay, S. V.; Manchoju, A. *J. Org. Chem.* **2012**, *77*, 10455.
(51) (a) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454. (b) Donner, C. D. *Tetrahedron Lett.* **2007**, *48*, 8888.
(52) Iwai, Y.; Kora, A.; Takahashi, Y.; Hayashi, T.; Awaya, J.; Masuma, R.; Oiwa, R.; Omura, S. *J. Antibiot.* **1978**, *31*, 959.
(53) Fernandes, R. A.; Mulay, S. V. *Tetrahedron: Asymmetry* **2013**, *24*, 1281.
(54) Wang, L.; Dong, J. Y.; Song, H. C.; Shen, K. Z.; Wang, L. M.; Sun, R.; Wang, C. R.; Gao, Y. X.; Li, G. H.; Li, L.; Zhang, K. Q. *Planta Med.* **2009**, *75*, 1339.
(55) Mulay, S. V.; Gholap, S. P.; Fernandes, R. A. *Asian J. Org. Chem.* **2015**, *4*, 560.
(56) Singh, S. B.; Cordingley, M. G.; Ball, R. G.; Smith, J. L.; Dombrowski, A. W.; Goetz, M. A. *Tetrahedron Lett.* **1991**, *32*, 5279.
(57) Gwaltney, J. M. Jr. In *Viral Infection of Man: Epidemiology and Control, 2nd ed*; Evans, E. A., Ed.; Plenum Publishing Co: New York, **1982**, 491.
(58) (a) Donner, C. D.; Gill, M. *Tetrahedron Lett.* **1999**, *40*, 3921. (b) Donner, C. D.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938.
(59) Mulay, S. V.; Bhowmik, A.; Fernandes, R. A. *Eur. J. Org. Chem.* **2015**, 4931.
(60) (a) Brockmann, H.; Pini, H. *Naturwissenschaften* **1947**, *34*, 190. (b) Brockmann, H.; Pini, H.; von Plotho, O. *Chem. Ber.* **1950**, *83*, 161. (c) Brockmann, H.; Loeschcke, V. *Chem. Ber.* **1955**, *88*, 778. (d) Brockmann, H.; Hieronymus, E. *Chem. Ber.* **1955**, *88*, 1379. (e) Brockmann, H.; Müller, W.; van der Merwe, K. *Naturwissenschaften* **1962**, *49*, 131. (f) Zeeck, A.; Christiansen, P. *Justus Liebigs Ann. Chem.* **1969**, *724*, 172. (g) Brockmann, H.; Zeeck, A.; van der Merwe, K.; Müller, W. *Justus Liebigs Ann. Chem.* **1966**, *698*, 209. (h) Christiansen, P. *Ph.D. Thesis*; University of Göttingen: Germany, **1970**. (i) Krone, B.; Zeeck, A. *Liebigs Ann. Chem.* **1987**, 751.
(61) Nelson, R. A.; Pope, J. A. Jr.; Luedemann, G. M.; McDaniel, L. E.; Schaffner, C. P. *J. Antibiot.* **1986**, *39*, 335.
(62) Ling, D.; Shield, L. S.; Reinhart, K. L. Jr. *J. Antibiot.* **1986**, *39*, 345.
(63) (a) Zhai, L.; Shukla, R.; Wadumethrige, S. H.; Rathore, R. *J. Org. Chem.* **2010**, *75*, 4748. (b) Boden, N.; Bushby, R. J.; Lu, Z.; Headdock, G. *Tetrahedron Lett.* **2000**, *41*, 10117. (c) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730. (d) Sperry, J.; Sejberg, J. J. P.; Stiemke, F. M.; Brimble, M. A. *Org. Biomol. Chem.* **2009**, *7*, 2599. (e) Laatsch, H. *Liebigs Ann. Chem.* **1987**, 297.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(64) Qu, C.; Tang, E.; Loeppky, R.; Deng, Z.; Pulley, S. R.; Hong, X. *Chirality* **2015**, *27*, 18.
(65) (a) Takano, S.; Hasuda, K.; Ito, A.; Koide, Y.; Ishii, F. *J. Antibiot.* **1976**, *29*, 765. (b) Nakagawa, A.; Fukamachi, N.; Yamaki, K.; Hayashi, M. Oh-ishi S.; Kobayashi, B.; Ōmura, S. *J. Antibiot.* **1987**, *40*, 1075.
(66) Hirose, T.; Kojima, Y.; Matsui, H.; Hanaki, H.; Iwatsuki, M.; Shiomi, K.; Ōmura, S.; Sunazuka, T. *J. Antibiot.* **2017**, *70*, 574.
(67) (a) Ōmura, S.; Takahashi, Y.; Kim, Y.-P.; Hanaki, H.; Koda, H.; Suzuki, M.; Shiomi, K. JP2009046404A, **2009**. (b) *Splendid Gifts from Microorganisms, 5th ed*; Ōmura, S., Ed.; The Kitasato Institute: Tokyo, **2015**, 243–245.
(68) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996.
(69) Sie, C.-J.; Patteti, V.; Yang, Y.-R.; Mong, K.-K. T. *Chem. Commun.* **2018**, *54*, 1885.
(70) (a) Korynevska, A.; Matselyukh, B. P.; Stoika, R. *Exp. Oncol.* **2003**, *25*, 98. (b) Korynevska, A.; Heffeter, P.; Matselyukh, B.; Elbling, L.; Micksche, M.; Stoika, R.; Berger, W. *Biochem. Pharmacol.* **2007**, *74*, 1713. (c) Lekha, L. V.; Panchuk, R. R.; Berger, W.; Rohr, J.; Stoika, R. S. *Ukr. Biochem. J.* **2015**, *87*, 72. (d) Crow, R. T.; Rosenbaum, B.; Smith, R. III.; Guo, Y.; Ramos, K. S.; Sulikowski, G. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1663.
(71) (a) Kharel, M. K.; Pahari, P.; Shepherd, M. D.; Tibrewal, N.; Nybo, S. E.; Shaaban, K. A.; Rohr, J. *Nat. Prod. Rep.* **2012**, *29*, 264. (b) Ostash, B.; Korynevska, A.; Stoika, R.; Fedorenko, V. *Mini-Rev. Med. Chem.* **2009**, *9*, 1040. (c) Henkel, T.; Rohr, J.; Beale, J.; Schwenen, L. *J. Antibiot.* **1990**, *43*, 492. (d) Luzhetskyy, A.; Zhu, L.; Gibson, M.; Fedoryshyn, M.; Durr, C.; Hofmann, C.; Hoffmeister, D.; Ostash, B.; Mattingly, C.; Adams, V.; Fedorenko, V.; Rohr, J.; Bechthold, A. *ChemBioChem* **2005**, *6*, 675.
(72) Bhowmik, A.; Fernandes, R. A. *Asian J. Org. Chem.* **2019**, *8*, 1534.
(73) (a) Lessmann, H.; Krupa, J.; Lackner, H. *Z. Naturforsch., B* **1989**, *44*, 353. (b) Taguchi, T.; Ebizuka, Y.; Hopwood, D. A.; Ichinose, K. *Tetrahedron Lett.* **2000**, *41*, 5253. (c) Ozawa, M.; Taguchi, T.; Itoh, T.; Ebizuka, Y.; Booker-Milburn, K. I.; Stephenson, G. R.; Ichinose, K. *Tetrahedron* **2003**, *59*, 8793. (d) Taguchi, T.; Okamoto, S.; Lezhava, A.; Li, A.; Ochi, K.; Ebizuka, Y.; Ichinose, K. *FEMS Microbiol. Lett.* **2007**, *269*, 234.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.