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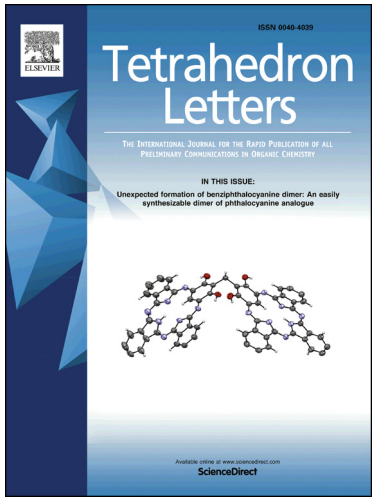

Digest paper

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Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

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Abstract: The cochliomycins (**7**-**12**) are a group of six resorcylic acid lactones that have recently been isolated from culture broths of marine fungi found in the South China Sea. These natural products have attracted attention as synthetic targets because of (in certain instances) their novel structural features and their capacities to supress biofouling. This short review summarizes the synthesis of these and certain related compounds that have been reported to date, including those developed in the authors' laboratories.

Contents

Introduction

The value of small molecule natural products (SMNPs) as therapeutic agents, as precursors to such agents or as the inspirations for them is well known.[1] Indeed, there are now indications that SMNPs, perhaps especially ones derived from marine environments,[2] are enjoying something of a renaissance not least because of their enormous structural diversity and their occupation of unique parts of chemical space.[3] Among the plethora of different natural product classes, the resorcylic acid lactones (RALs) are notable for the frequency with which they are isolated from fungal

sources, their distinctive structural features and their breadth of biological activities.[4] In the following section an overview of the structural variations within the RAL class is provided along with a brief commentary on the source organisms and certain of their biological properties. As a recently discovered and interesting subset of RALs that has not been the subject of any previous reviews, the cochliomycins are then described and a summary of the synthetic work carried out on them follows.

Resorcylic Acids Lactones (RALs) as a Natural Product Class

The RALs are mycotoxins and the products of a distinctive polyketide biosynthesis that exploits an acetyl CoA starter unit together with malonyl-CoA extenders and involves two fungal polyketide synthases (PKS) that work co-operatively.[4e] Specifically, a non-reducing PKS is coupled with highly reducing one that enables the assembly of the relevant resorcylic acid core annulated to a 14-membered macrolactone (and wherein most of the structural variation resides). Unsurprisingly perhaps, the final step in the biosynthesis is the macrolactonisation event that releases the substrate from the enzyme complex. Post-PKS-mediated processes such as epoxidation, halogenation and alkylation may then follow so as to provide the fully "decorated" (isolated) metabolite.[4e]

Radiciol (**1**) was the first RAL to be isolated (from *Monosporium nordinii*) and characterised in the 1950s[4] and it has since been obtained from various other fungal strains. In the intervening period numerous other RALs have been identified and these vary in the nature of the substitution pattern on the aromatic ring as well as the location and degree of unsaturation and/or oxygenation within the macrolactone ring. The structures of the RALs hypothemycin (**2**), zearalenone (**3**), pochonin C (**4**), L-783,277 (**5**) and aigialomycin D (**6**) shown in Figure 1 serve to highlight such degrees of variation.

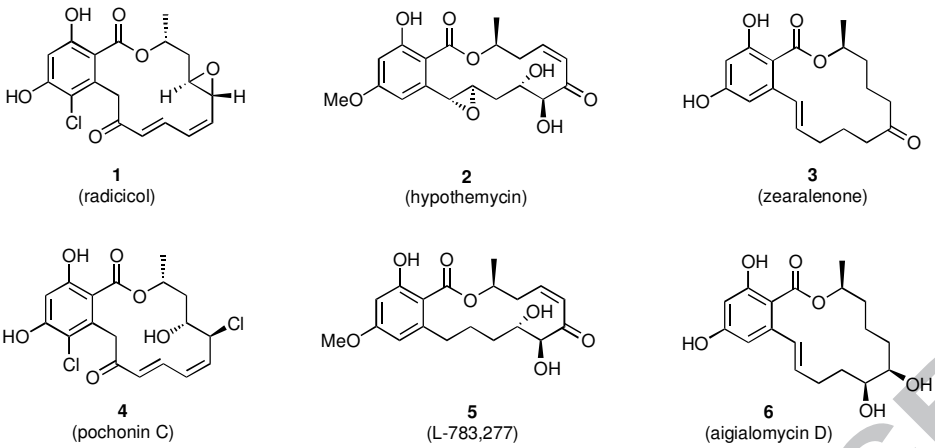


Figure 1: Examples of the Structural Variations Possible Within the RAL Class

Initial biological evaluation of radiciol (**1**) showed it to possess anti-bacterial properties and to act as a mild sedative. However, the later revelation that it acts as a powerful inhibitor of heat shock protein 90 (HSP90) - and thus representing an important lead in the development of oncolytic agents - caused much greater attention to be given to the RALs. In contrast to radiciol (**1**), the *cis*-enone-containing hypothemycin (**2**) has been shown to strongly inhibit the kinase MEK1 while zearalenone (**3**) acts as an estrogen agonist and its hormone-like properties have been shown to promote growth in cattle and sheep. A closely related RAL is now commercially available and employed to alleviate post-menopausal stress in women and as an anabolic cattle-growth stimulant. Pochonin C (**4**), on the other hand, inhibits herpes simplex virus (HSV) replication in a potentially therapeutically useful way while the *cis*-enone L-783,277 (**5**), like congener **2**, inhibits MEK1. Aigialomycin D (**6**), despite the absence of a *cis*-enone moiety, also acts as a kinase inhibitor as well as an anti-malarial agent (the latter property seemingly being unrelated to the former).

The Discovery of Cochliomycins A-F

In papers published in 2011[5] and 2014,[6] Wang and co-workers from the Ocean University of China in Qingdao reported the isolation of cochliomycins A-F (**7**-**12**) (Figure 2) from the culture broths of *Cochliobolus lunatus* (M351) or *C. lunatus* (TA26-46), fungi associated with the gorgonian *Dichotella gemmacea* or the sea anemone *Palythoa haddoni*, respectively. Both host organisms were collected in the

South China Sea. The structures of these RALs were established through the application of the usual battery of spectroscopic methods and the absolute stereochemistries of the last three determined using the CD exciton chirality method in conjunction with TDDFT ECD calculations.[6]

The most striking features of this subset of RALs are the presence of acetonide units within the structures of congeners A and B (**7** and **8**, respectively). Since acetone was not used in the isolation, purification or spectroscopic characterisation of these compounds they must be considered as natural products rather than artefacts. Wang and co-workers also noted[5] that on standing in $CDCl_3$ at ambient temperatures cochliomycin B (**8**) slowly isomerised to congener **7** and so suggesting the latter is the thermodynamically more stable compound. Cochliomycin C (**9**) is the only member of the series lacking a second double bond within the macrocylic ring. Cochliomycins D (**10**) and E (**11**) are isomeric while congener F (**12**) is not simply a chlorinated derivative of one or other of the first two because of the differing configuration at one or other of the hydroxyl-bearing methine carbons. Nor, for the same reasons, can colchliomycin F (**12**) simply be the product of the two-fold oxidation of congener **9**.

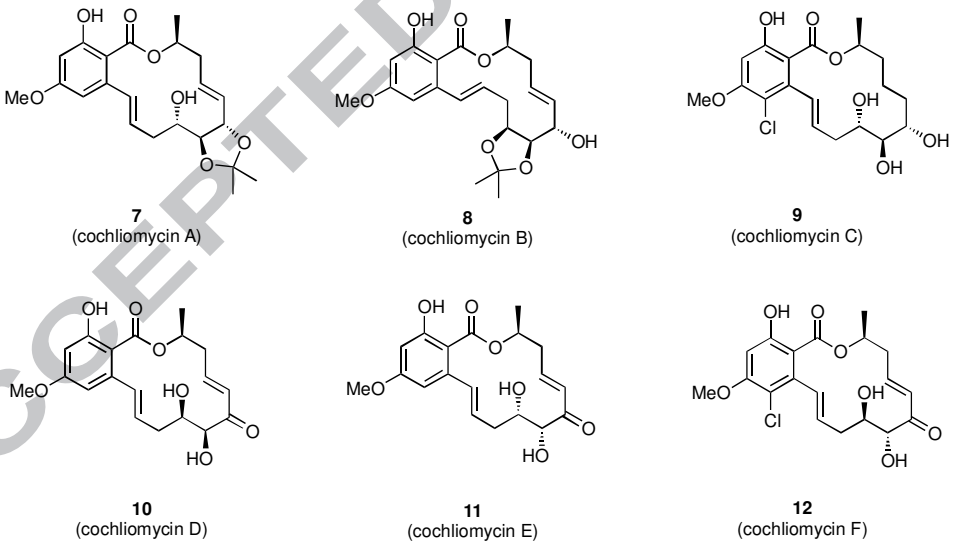


Figure 2: The Structures of Cochliomycins A-F (**7**-**12**, respectively).

Related, Co-occurring Natural Products

In the course of structurally characterizing the cochliomycins, it was noted[5] that congener C (**9**) is the chlorinated derivative of co-isolated paecilomycin F (**13**) (Figure 3), a previously reported RAL that displays anti-malarial properties. Other RALs also isolated alongside compounds **7**-**9** were zeaenol (**14**), LL-Z1640-1 (**15**) and LL-Z1640-2 (**16**). During the course of isolating cochliomycins D, E and F (**10**, **11** and **12**, respectively), cochliomycin A (**7**), zeaenol (**14**), LL-Z1640-1 (**15**), LL-Z1640-2 (**16**), its *E*-isomer **17** [(7′*E*)-6′-oxozeaenol], deoxyaigialomycin C (**18**) and aigialomycin B (**19**) were also observed in the mixture of isolates. Clearly certain of these co-isolates are isomeric with the cochliomycins or otherwise closely related. For example, zeaenol (**14**) is the acetonide "deprotected" analogue of cochliomycins A (**7**) and B (**8**).

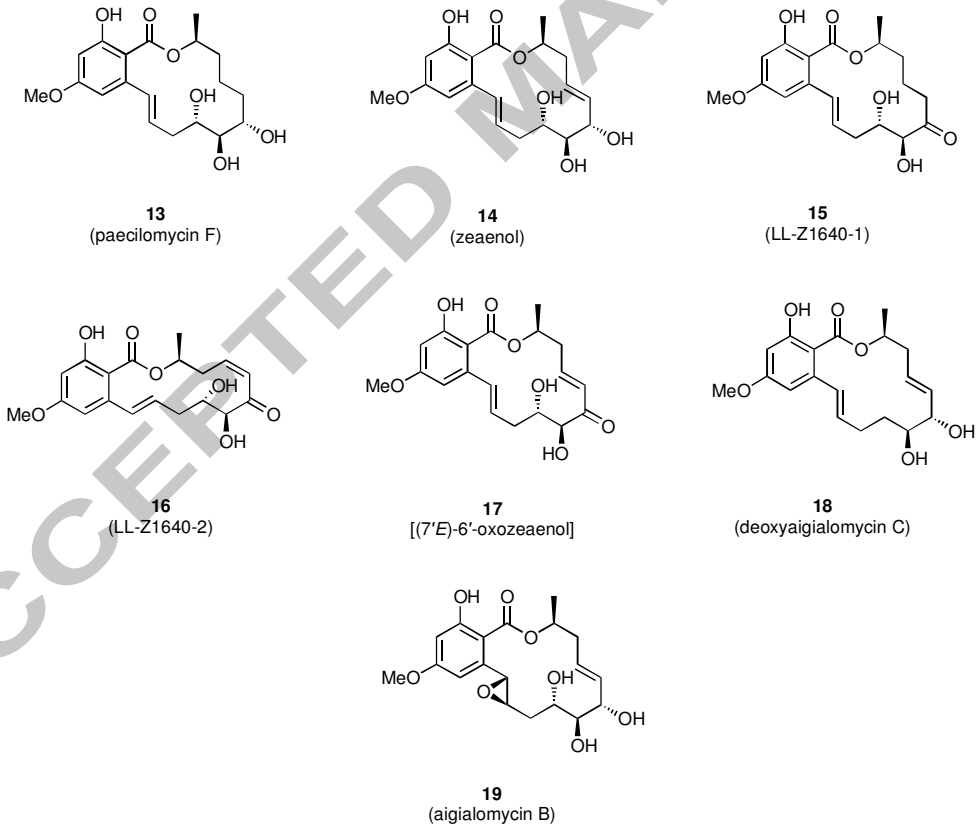


Figure 3: The Structures of RALs Found to Co-occur with Cochliomycins A-C and/or Cochliomycins D-E

Biological Properties of the Cochliomycins

The most notable biological properties of at least certain of the colchiomycins are their anti-fouling properties. So, for example, on evaluating the effects of cochliomycins A-C (**7**-**9**) on the larval settlement of the barnacle *Balanus amphitrite*, the first of these completely inhibited this process at concentrations of 20.0 μg/mL and still displayed significant effects at 5.0 μg/mL. Zeaenol (**14**) and compound **7** as well as two acetate derivatives of the latter displayed potent anti-fouling activities at non-toxic concentrations with EC_{50} values of 5.0, 1.2, 15.4 and 12.5 μg/mL, respectively. These values are well below the threshold requirement (EC_{50} 25 μg/mL) set by the US Navy program as an efficacy level for the development of natural anti-fouling agents. Given the structural relationship between compounds **7** and **14**, the presence of the acetonide moiety in the former compound clearly has a beneficial effect on anti-fouling properties. Furthermore, since these same compounds display high therapeutic ratios they might well be useful as environmentally benign anti-fouling agents. Cochliomycin A's anti-fouling effects are now thought to arise through stimulation of the NO/cGMP pathway in the cyprid lavael phase of the barnacle's lifecycle.[7] The subsequent evaluation of cochliomycins D, E and F revealed that the first and third of these also displayed potent anti-fouling effects at non-toxic concentrations (EC_{50} values of 17.3 and 6.67 μg/mL, respectively).[6] Significantly, the most active compound among the isolates from the culture broth of *C. lunatus* (TA26-46) was the *cis*-enone-containing LL-Z1640-2 (**16**). The EC_{50} value of this compound (1.82 μg/mL) is close to that of the commercially employed anti-fouling agent SeaNine 211™ (1.23 μg/mL)[8] but has a significantly more favourable therapeutic ratio [LC_{50}/EC_{50} >50 (for **16**) *vs* 20.3]. The differing anti-fouling behaviours of cochliomycins D, E and F suggest that variations in stereochemistry can have a notable impact on activity.

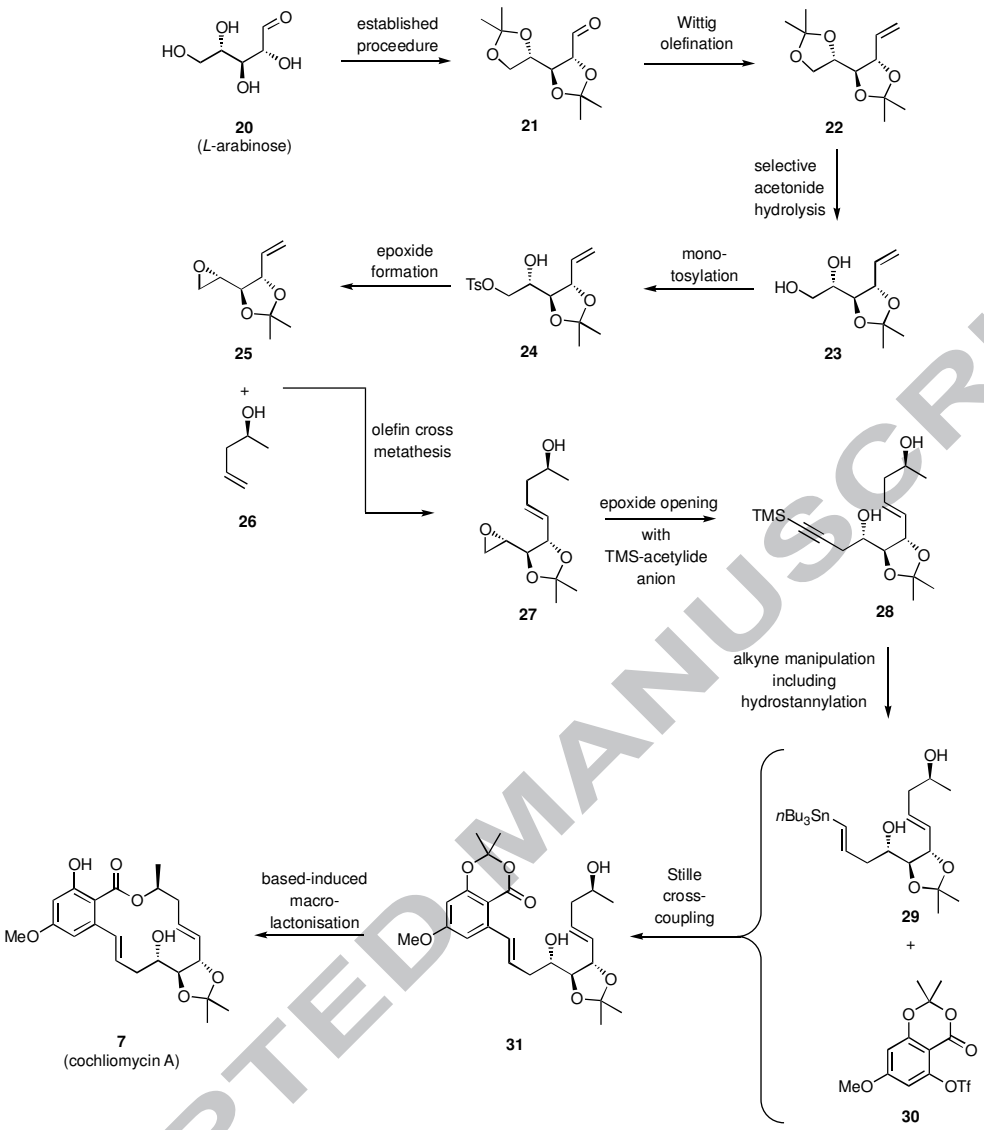
Interestingly, cochliomycin A (**7**) displayed moderate anti-bacterial activity against *Staphylococcus aureus*[5] while, unlike cochliomycins D, E and F, LL-Z1640-2 (**16**) displayed potent inhibitory effects against various pathogenic fungi.[6]

Synthetic Studies on the Cochliomycins

As with other RALs, the cochliomycins have been the subject of various synthetic studies, both for the purposes of confirming their structures and as a means of providing more material (as well as analogues). Almost invariably, a major consideration in such work is the manner in which the 14-membered lactone ring is closed. A range of methods has been successfully employed for this purpose and these are presented within the individual descriptions given below of the various syntheses reported to date.

(a) The Du Group Syntheses

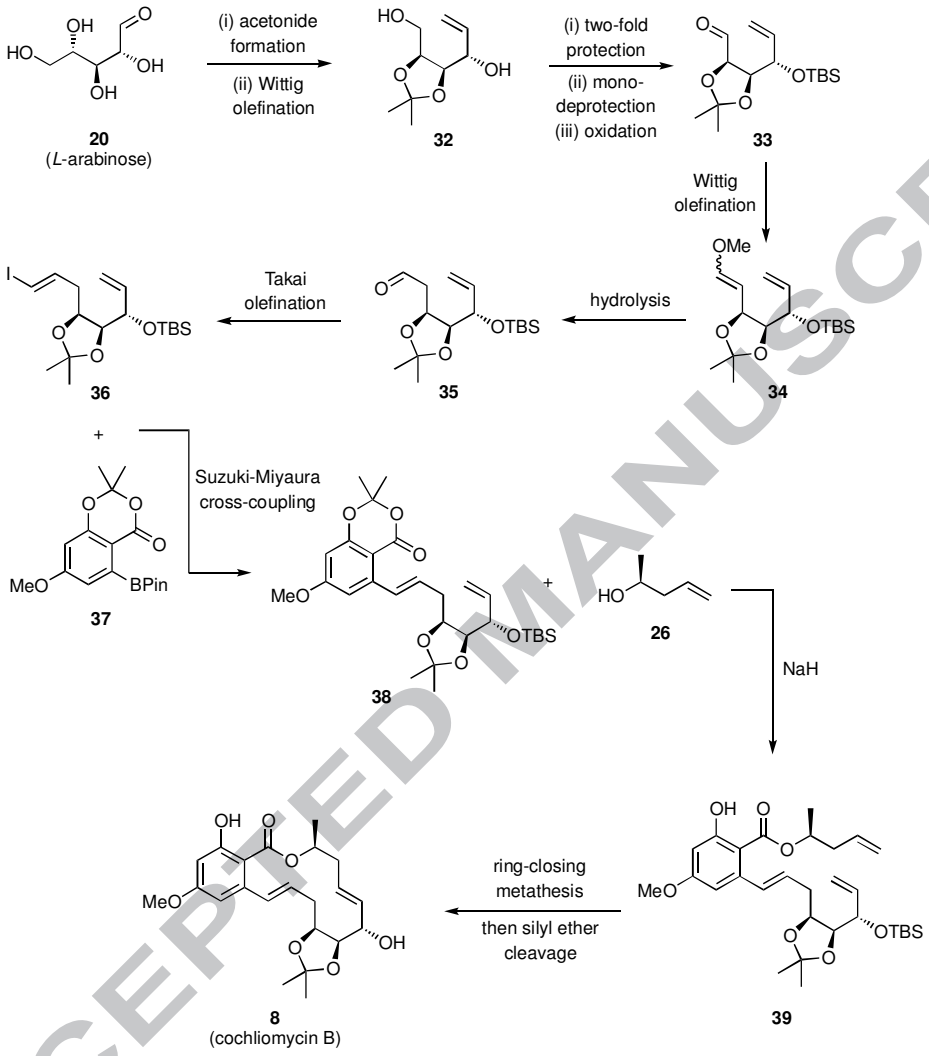
The Du group's synthesis of cochliomycin A (**7**) was reported[9] in 2014 and employed *L*-arabinose as the chiron for assembling the three contiguous stereogenic centres within the macrolide along with a base-promoted lactonisation reaction to close the ring itself. The detailed reaction sequence is shown in Scheme 1 and started with the conversion of *L*-arabinose (**20**) into the corresponding *bis*-acetonide (**21**) under standard conditions and the latter compound subjected a Wittig olefination (to give **22**) and then selective acetonide hydrolysis using aqueous acetic acid. Diol **23** so-formed (77% from **21**) was selectively tosylated and ester **24** then treated with base so as to form epoxide **25** (78% from **23**). Olefin cross-metathesis of compound **25** with the commercially available and *S*-configured alcohol **26** gave the *E*-alkene **27** (85%) and the associated epoxide ring then opened using the anion derived from trimethylsilylacetylene and thus producing the homopropargylic alcohol **28** (78%).



Scheme 1: The Du Group Synthesis of Cochliomycin A (**7**)

Over three steps, including a Pd-catalysed hydrostannylation reaction, the acetylenic unit associated with compound **28** was converted into the alkenylstannane **29** (71%) that was itself engaged in a Stille cross-coupling with the well known aryl triflate **30** and thus producing compound **31** (81%), the immediate precursor to target **7**. Indeed, on treatment with sodium hydride in DMF the conversion **31** → **7** was effected in 46% yield.

The Du Group's synthesis of cochliomycin B (**8**) (Scheme 2)[10] also started with *L*-arabinose but a ring-closing metathesis reaction was now used to construct the associated macrolide ring.



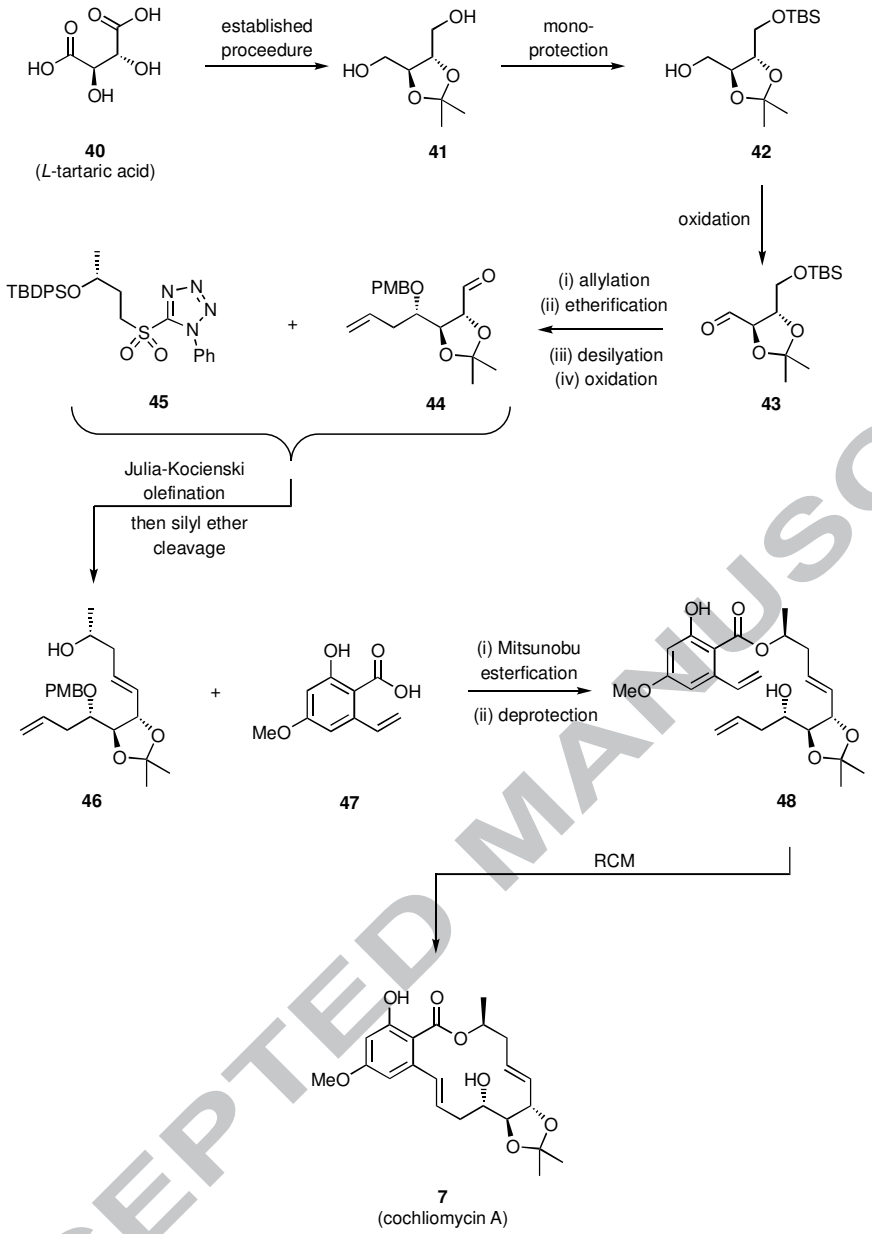
Scheme 2: The Du Group Synthesis of Cochliomycin B (**8**)

Thus, compound **20** was converted, under conventional conditions, into the corresponding 3,4-mono-acetonide and this itself subject to a Wittig olefination reaction and so affording compound **32** (72%). Over three steps this diol was manipulated so as to generate aldehyde **33** (46%) and a Wittig-based homologation of this last compound afforded, *via* enol ether **34** (77%), congener **35** (75%). Takai-type olefination of this last compound then gave the *E*-configured iodoalkene **36** (53%)

that was engaged in a Suzuki-Miyaura cross-coupling with the readily obtained arylboronate **37** and so affording the *trans*-styrene **38** (68%). Reaction of this last compound with the anion derived from homochiral alcohol **26** then gave ester **39** (75%) that upon reaction with Grubbs' second generation catalyst afforded, *via* ring-closing metathesis (RCM), the required macrocycle (67%) and treatment of this with tetra-*n*-butylammonium fluoride (TBAF) then gave cochliomycin B (**8**) in 85% yield. Interestingly, in the penultimate step there was no competing RCM involving the styrenyl double bond and the proximate terminal olefin (a process that would lead to side-chain fragmentation and formation of a cyclohexene).

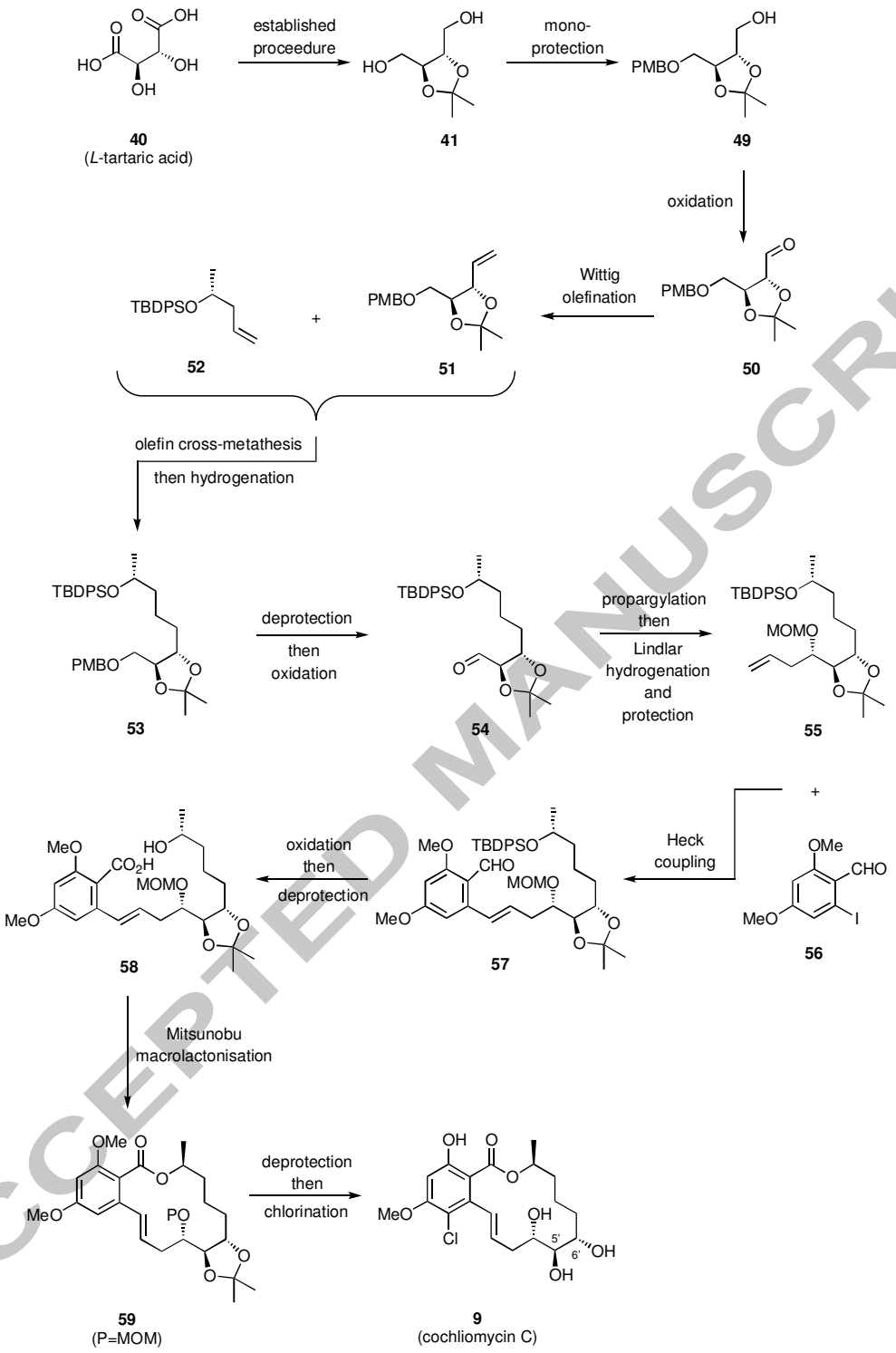
(b) The Nanda Group Syntheses

Jana and Nanda reported a synthesis of cochliomycin A in 2012[11] and this started with the conversion, by well established methods, of *L*-(+)-tartaric acid (**40**) into 2,3-di-*O*-isopropylidene-*L*-threitol (**41**) and mono-protection of the latter to give ether **42** (85%). Oxidation of compound **42** under Swern conditions gave the corresponding aldehyde **43** (90%) that was subjected to a highly diastereoselective Keck asymmetric allylation reaction and so affording, after protection of the resulting homoallylic alcohol, cleavage of the TBS ether and oxidation of the resulting alcohol, aldehyde **44** (59%). A Julia-Kocienski olefination reaction was then carried out on compound **44** using the readily prepared sulfone **45**, KHMDS and 18-crown-6 and so affording, in a highly selective manner and after silyl ether cleavage, the target *E*-alkene **46** in 75% yield. Mitsunobu coupling of this last compound with acid **47** then gave, after cleavage of the PMB ether residue, ester **48** (73%). Upon exposure to Grubbs' second-generation catalyst compound **48** was converted into cochliomycin A (**7**) (72%).



Scheme 3: The Nanda Group Synthesis of Cochliomycin A (**7**)

The Nanda Group synthesis of cochliomycin C[12] (Scheme 4) also started with *L*-tartaric acid (**40**) and exploited a Mitsunobu-mediated lactonisation reaction to form the macrolide ring. Specifically, then, di-acid **40** was, once again, converted into the diol-acetonide **41** and the latter mono-protected as the corresponding *p*-methoxybenzyl (PMB) ether **49** (85%). Upon Swern oxidation this last compound gave the aldehyde **50** (90%), Wittig olefination of which afforded the terminal olefin **51** (70-75%) that was subjected to an olefin cross-metathesis (OCM) reaction with the unsaturated and homochiral ether **52** using the Grubbs' second-generation catalyst.



Scheme 4: The Nanda Group Synthesis of Cochliomycin C (**9**)

The primary product of this process was then hydrogenated under conventional conditions so as to give compound **53** (79%). Oxidative cleavage of the PMB-ether

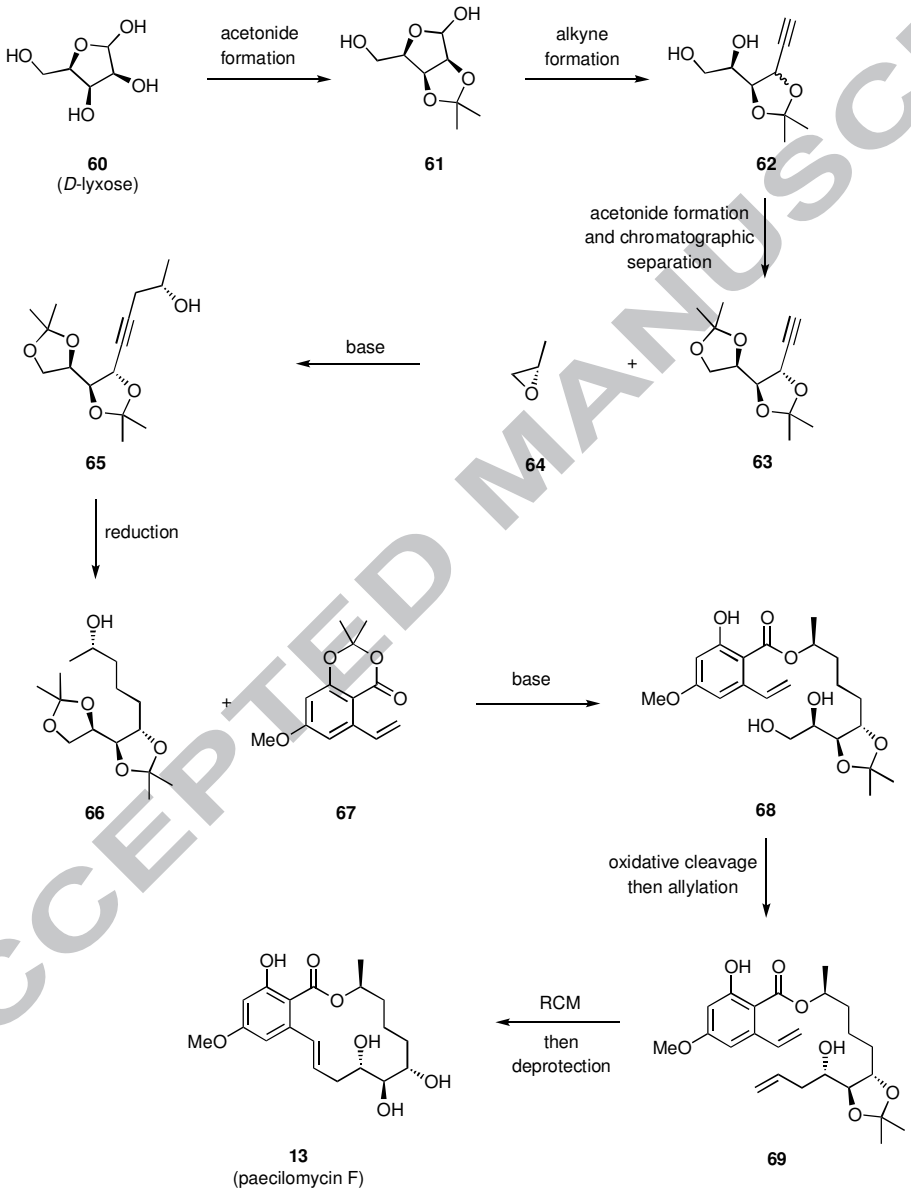
residue associated with bis-ether **53** then gave the corresponding alcohol that was oxidised to aldehyde **54** (80%) using the Dess-Martin periodinane. Reaction of compound **54** with the propargyl anion proceeded stereoselectively and Lindlar hydrogenation of the product alkyne gave the corresponding homoallylic alcohol that was protected as the MOM-ether **55** (78%). Heck coupling of the last compound with the iodinated benzaldehye **56** afforded styrene **57** (84-90%) and oxidation of the associated aldehyde residue gave the corresponding benzoic acid. Cleavage of the TBDPS-ether within product **57** then afforded the substrate **58** (61-79%) used in the macrolactonisation reaction. So, compound **58** was subjected an intramolecular Mitsunobu reaction that provided macrolide **59** (P = MOM) (78%), the MOM-group of which was cleaved and the product RAL, *viz*. paecilomycin F (**13**), was then chlorinated using sulfuryl chloride and thus affording cochliomycin C (**9**) in 71% yield.

Nanda and his colleagues have also reported[13,14] related syntheses of the C5′- and C6′-epimers of cochliomycin C.

(c) The Srihari Group Approach

The Srihari Group synthesis of cochliomycin C (**9**)[15] (Scheme 5) is a formal one [in that it delivers paecilomycin F (**13**)], relies on *D*-lyxose (**60**) as starting material and uses a RCM reaction to construct the macrolide ring. The synthesis starts with the conversion of compound **60** into the previously reported mono-acetonide **61** (95%) and this was subjected to an Ohira-Bestmann alkyne forming reaction that delivered, with accompanying epimerisation, compound **62** (49%) as a mixture of diastereoisomers. Conversion of this last pair of compounds into the corresponding bis-acetonides and chromatographic separation of the major product **63** (45%) was followed by the regioselective reaction of the derived anion with the commercially available and homochiral epoxide **64** and so affording the 2°-alcohol **65** (82%). Exhaustive reduction of the alkyne moiety associated with this last compound and reaction of the oxyanion derived from product **66** (86%) with the readily prepared arene **67** then gave, after acid treatment, the vinylated salicylate **68** (65%). This was subject to oxidative cleavage and the ensuing aldehyde allylated in a diastereoselective manner to give diene **69** (63%). Compound **69** was then engaged in

a RCM reaction using the Hoveyda-Grubbs second generation catalyst and by such means, and after cleavage of the associated acetonide residue, paecilomycin F (**13**) was obtained in 68% yield. Since Nanda[12] has previously converted compound **13** into cochliomycin C (**9**) through electrophilic aromatic chlorination using sulfuryl chloride a formal total synthesis of the latter natural product was realised in this instance.



Scheme 5: The Srihari Group Synthesis of Paecilomycin F (**13**)

By related means C6′-*epi*-cochliomycin C was obtained.[15]

(d) Background to the Banwell Group Studies on the Synthesis of RALs

Our group's original efforts in the area arose through an interest in exploiting enzymatically-derived and homochiral *cis*-1,2-dihydrocatechols[16] such as **70** (Figure 4) in the assembly of various RALs. The pivotal building block employed for this purpose was Weinreb amide **71**[17] obtained through, *inter alia*, reduction of the non-halogenated double bond associated with the acetonide derivative of diol **70** and ozonolytic cleavage of the remaining (halogenated) one. Compound **71** served as a precursor to L-783,290 (**72**) and its *cis*-isomer **5**, the latter being, as noted above, a potent inhibitor of MEK1. While the macrolide ring and the *E*-configured C=C bond associated with target **72** was constructed using a RCM reaction, a more novel means of assembling the analogous (*Z*-configured) motif within congener **5** was developed.[18] Details are provided immediately below.

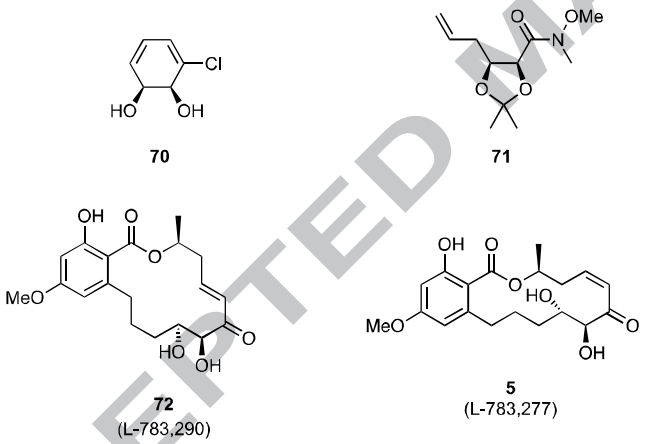
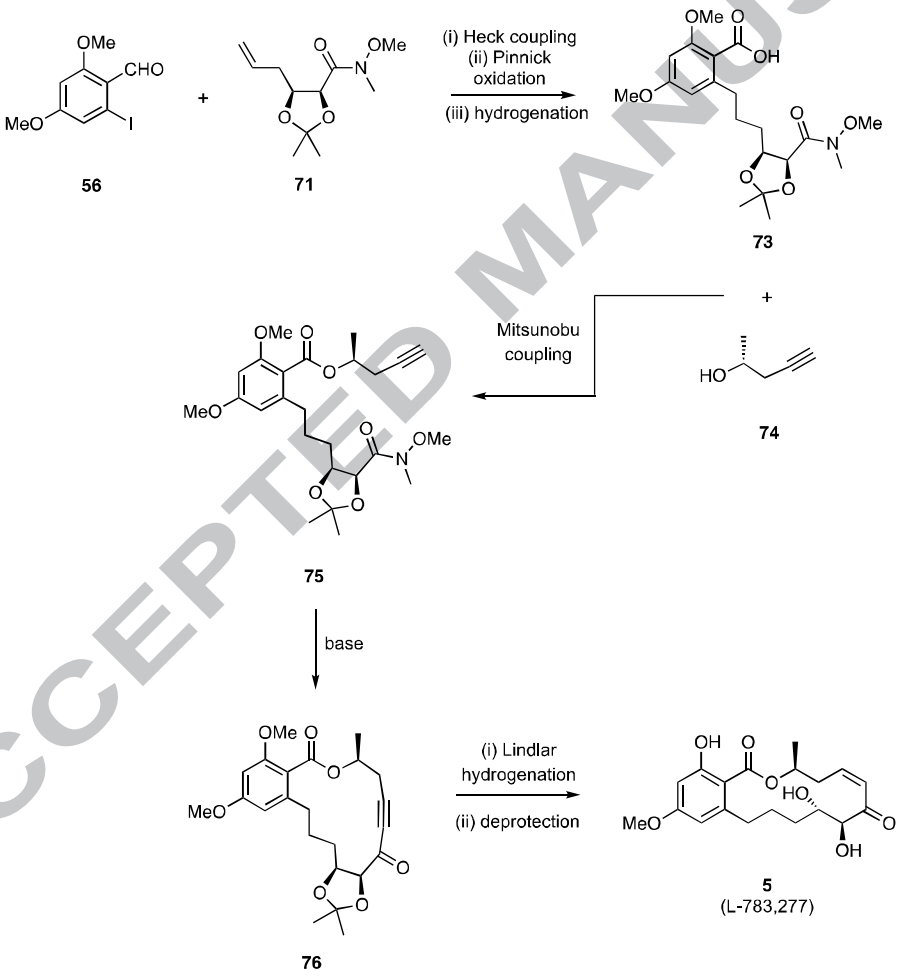


Figure 4: The starting material **70** and intermediate **71** used by the Banwell Group in establishing total syntheses of RAL L-783,290 (**72**) and its *cis*-isomer **5**.

Our synthesis of the *cis*-enone-containing L-783,277 (**5**) is shown in Scheme 6 and, like the pathway leading to congener **72**, involved, on the early stages, the Heck coupling of aryl iodide **56** with the unsaturated Weinreb amide **71**. The immediate product of this process was oxidised to the corresponding acid (under Pinnick conditions) and this then hydrogenated to give compound **73** (41%) that was, in turn, treated with the oxyanion derived from the homochiral propargylic alcohol **74** (itself

available through enzymatic resolution of the corresponding racemate). The ester **75** (70%) so formed was treated with potassium hexamethyldisilazide so as to generate the corresponding acetylide anion that itself engaged in an intramolecular acylation reaction and so producing the cyclic alkyne **76** (45%) and for which a single-crystal X-ray analysis was undertaken. This analysis revealed an essentially linear geometry about the internal triplet bond and thus highlighting the capacity of the 14-membered macrolide ring of RALs to accommodate a range of structural motifs. The completion of the synthesis of target **5** involved Lindlar-type hydrogenation of cyclisation product **76** and two-fold deprotection of the ensuing *cis*-enone gave L-783,277 (**5**) (40%) without compromising the integrity of the *Z*-configured double bond.

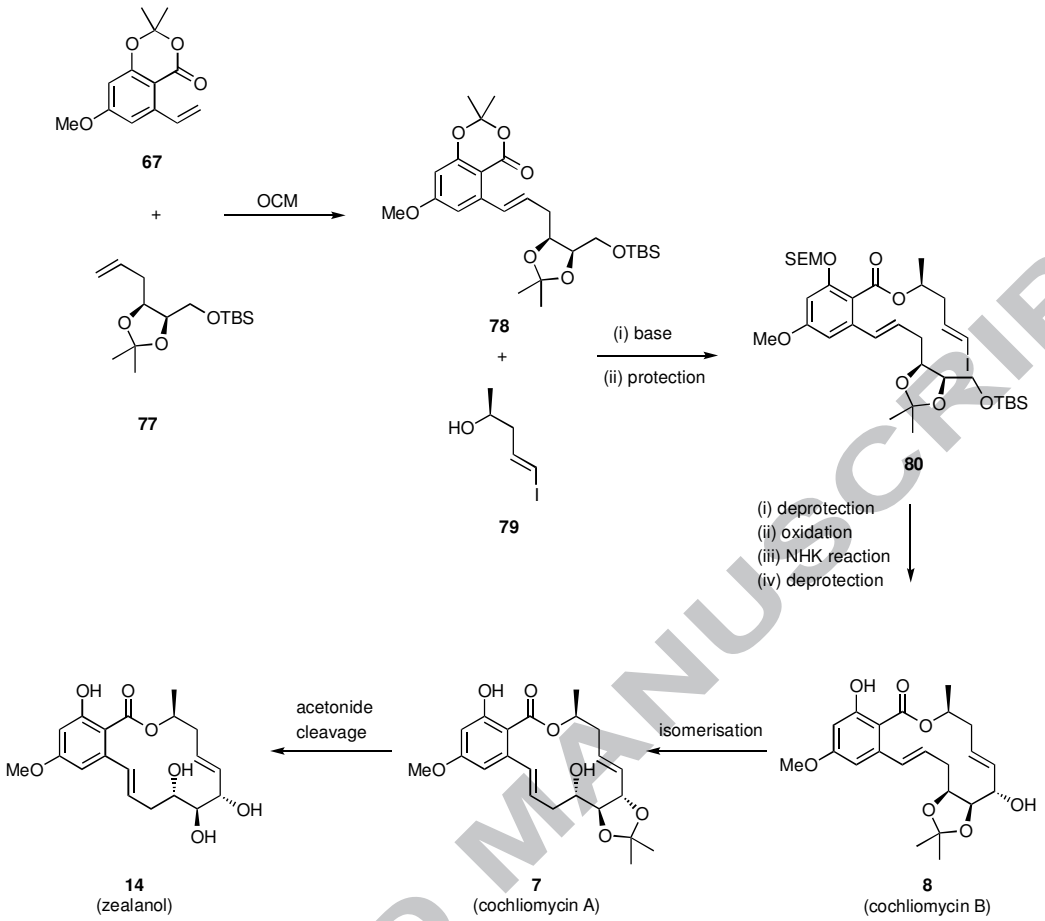


Scheme 6: The Banwell Group Synthesis of L-783,277 (**5**)

(e) The Banwell Group Syntheses

Our syntheses of RALs **5** and **72** were completed just prior to the report[5] of the isolation and structural characterisation of cochliomycins A-C (**7**-**9**, respectively). Given this, the presence of the (unusual) acetonide residues within congeners A and B and the novel biological properties they display we were attracted to developing syntheses of them. Our route[19] to the first two of these (*viz.* the acetonide-containing ones) exploited a late-stage and highly stereoselective Nozaki–Hiyama–Kishi (NHK)[20] reaction to effect the necessary macrocyclization process, a relatively unusual one in terms of its application in the synthesis of RALs.

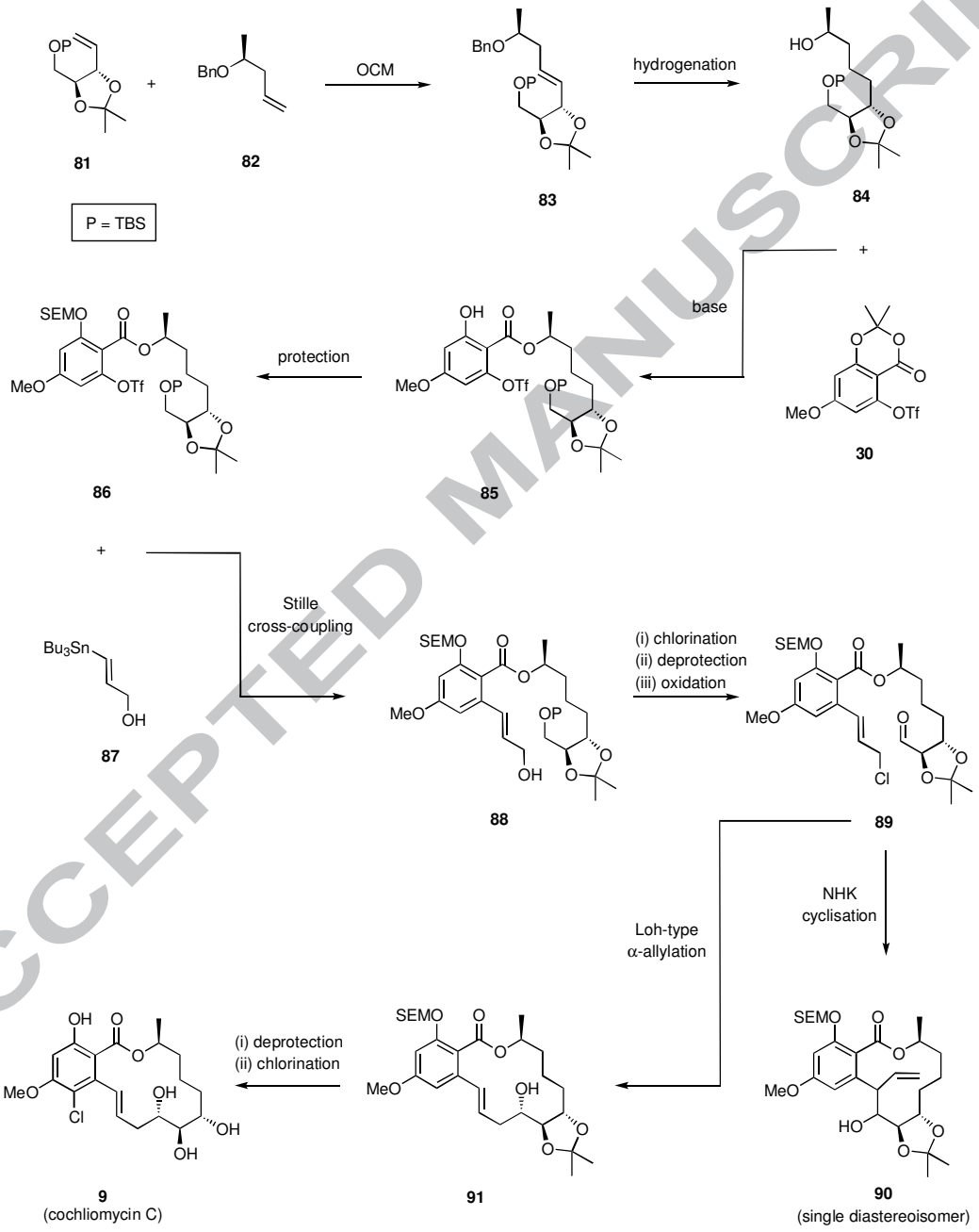
The pivotal elements of the synthetic sequence used are shown in Scheme 7 and involved an OCM of the readily available olefin **67** with the *D*-2-deoxyribose-derived and previously reported chiron **77** to give compound **78** (86%). The β-substituted styrene **78** was then reacted with the readily prepared homoallylic alcohol **79** in the presence of base and so affording, after protection of the phenolic OH group, the ester **80** (80%). Treatment of ester **80** with TBAF resulted in selective cleavage of the TBS-ether moiety and oxidation of the resulting and rather sensitive 1°-alcohol with the Dess-Martin periodinane then gave the corresponding aldehyde. This was immediately engaged in an intramolecular NHK reaction to afford, with high levels of diastereocontrol, the SEM ether of cochliomycin B (**8**) (77%). When this ether was treated with TBAF in refluxing THF then cochliomycin B (**8**) itself was obtained in 73% yield. In contrast, on treating the SEM ether with HCl in methanol at 22 °C for 1 h then congener A (**7**) (91%) was obtained while extended exposure of the same substrate to the same conditions resulted in acetonide group cleavage and formation of the previously reported RAL zeaenol (**14**) which was obtained in 84% yield.



Scheme 7: The Banwell Group Syntheses of Cochliomycins A and B

The end game associated with our approach[21] to cochliomycin C (**9**) was rather different and resulted in the identification of a new means for forming the macrolide ring of RALs. The reaction sequence started (Scheme 8) with an OCM reaction between the readily available alkenes **81** and **82** (the former compound being obtained from *L*-tartaric acid) and conventional hydrogenation of the product olefin **83** (88%) to give alkane **84** (98%). The anion derived from the last compound was reacted with arene **30** and thus affording ester **85** (91%), the phenolic group of which was protected as the corresponding SEM-ether **86** (94%). A Stille cross-coupling reaction between aryl triflate **86** and the alkenylstannane **87** then gave the cinnamyl alcohol **88** (76%) that was converted over three standard steps into the rather unstable aldehyde **89** (66%). Given our previous positive experiences with the NHK reaction we sought to apply this in the macrocyclisation of compound **89**. However, on exposing this a mixture of chromous chloride and nickel(II) chloride in DMF only the vinylated 12-

membered lactone **90** was obtained (as a single diastereoisomer in 33% yield). In stark contrast, when the same substrate was treated with indium in a mixture of water and dichloromethane then a Loh-type α-allylation reaction took place and so affording, in a highly diastereoselective manner, the 14-membered macrocycle **91** (61%).



Scheme 8: The Banwell Group Synthesis of Cochliomycin C

Removal of the acetonide and SEM protecting groups associated with this last compound using aqueous acid then gave paecilomycin F (**13**) that was chlorinated with sulfuryl chloride and so affording cochliomycin C (**9**) in 82% yield.

During the course of our work detailed above Cutler and colleagues reported[22] the isolation of three new RALs from a fungus *Neocosmospora* sp. (UM-031509). They were named neocosmosins A-C and structures **92**-**94** (Figure 5) respectively, assigned to them. These RALs were found to co-occur with three previously reported ones, namely radiciol (**1**), monocillin II (**95**) and monocillin IV (**96**). Unlike any of the RALs we had previously targeted for synthesis, all of the *Neocosmospora*-derived compounds embody a C10-keto residue and three of them (**1**, **94** and **95**) show good binding affinity for the human opioid receptors. Accordingly, we sought to develop a synthesis of the first of these, namely compound **92** and embodying the structure assigned to neocosmosin A.

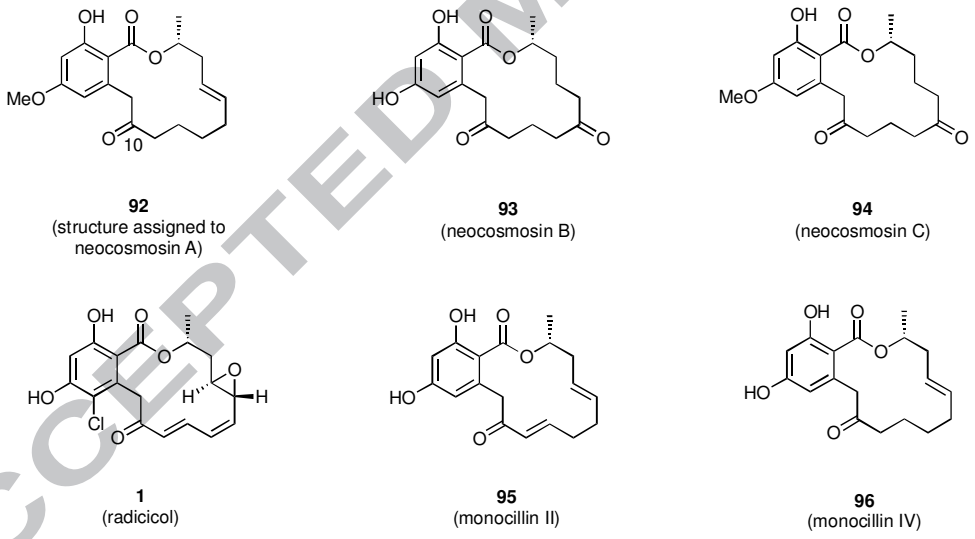
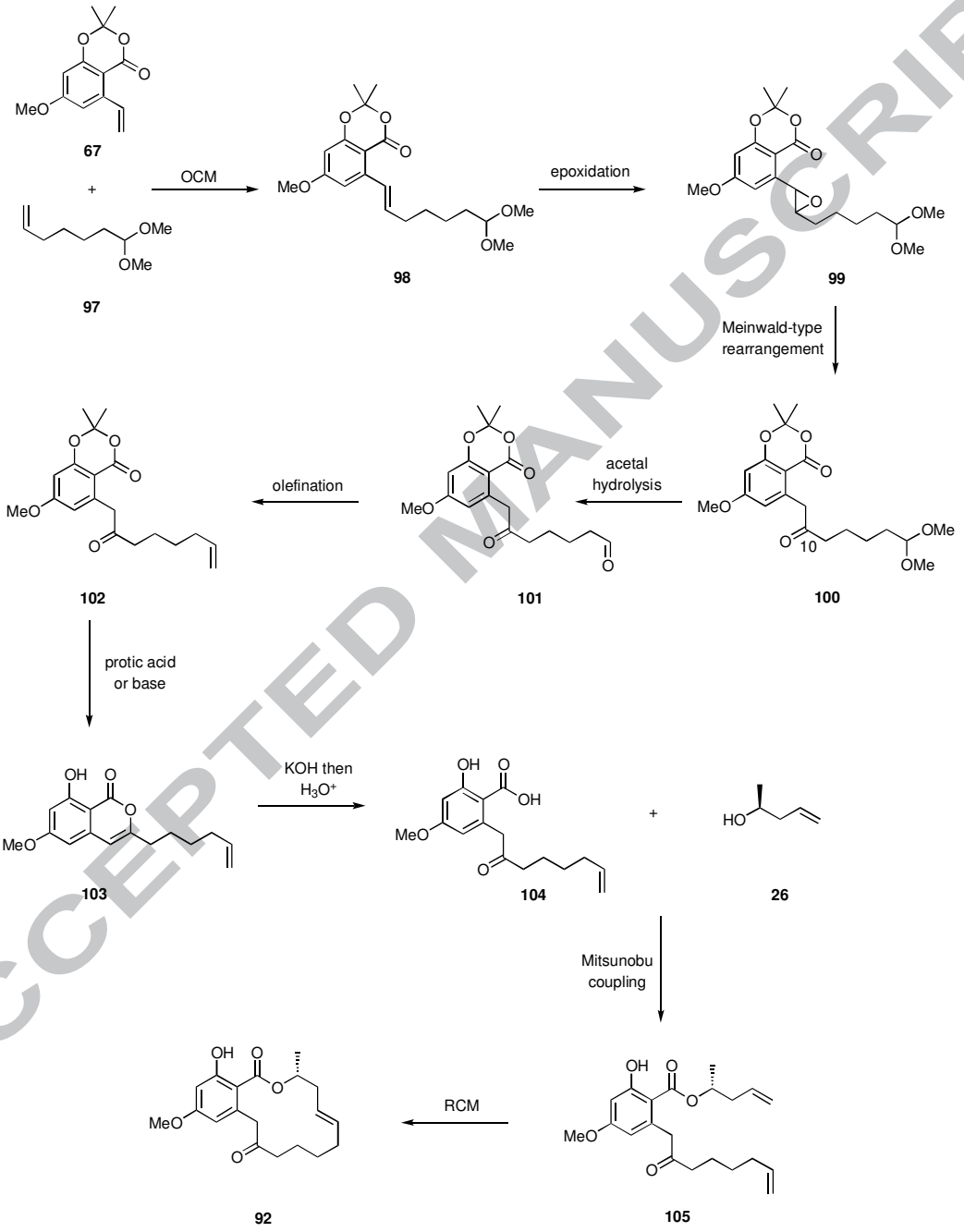


Figure 5: The Structures **92**-**94** Assigned to Neocosmosins A-C (respectively) and the Co-occurring RALs Radiciol (**1**), Monocillin II (**95**) and Monocillin IV (**96**).

Our synthesis of RAL **92**[23] is shown in Scheme 9 and began with the OCM of styrene **67** and the unsaturated acetal **97**. The product *E*-alkene **98** (72%) was treated with dimethyl dioxirane and the resulting epoxide **99** (quant.) engaged in a Meinwald-type rearrangement on exposure to $Pd(OAc)_2$ and *n*-Bu_3P and thus affording ketone **100**

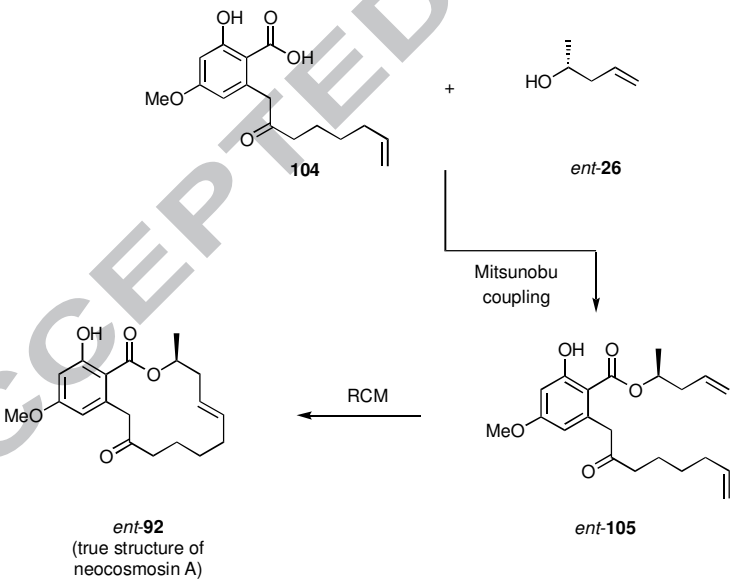
(88%) embodying the pivotal C10 carbonyl unit (RAL numbering) associated with the target **92**. Acid-catalysed hydrolysis of the acetal moiety within compound **100** afforded the corresponding keto-aldehyde **101** (89%) that could be selectively methylenated using the Wittig reagent and so giving the terminal alkene **102** (74%).



Scheme 9: The Banwell Group Synthesis of RAL **94**

Compound **102** was particularly prone to cyclisation on treatment with either acid or base. So, for example, when it was heated with *p*-TsOH in toluene in the presence of ethylene glycol (in an effort to prepare the corresponding ketal) then the unsaturated lactone **103** (82%) was formed but this could be cleaved with potassium hydroxide in aqueous THF and thus gave, after careful acidic work up, keto-acid **104** (96%). Compound **104** then served as the nucleophile in a Mitsunobu reaction with the homochiral 2°-alcohol **26** and thus affording the ester **105** (78%) that was itself engaged in a RCM reaction using Grubb's second generation catalyst and thus producing the target RAL **92** (83%). All of the NMR, IR and MS spectral data acquired on this product matched those reported for neocosmosin A. However, while the specific rotation of compound **92** was of a similar magnitude to that reported for the natural product it was of the opposite sign. As such we concluded that the absolute configuration of neocosmosin A had been incorrectly assigned and is, in fact, represented by structure *ent*-**92**.

The synthesis of compound *ent*-**92** (Scheme 10) involved a trivial adaptation of the process shown above.



Scheme 10: The Banwell Group Synthesis of the True Structure of Neocosmosin A (*ent*-**92**).

Thus, Mitsunobu coupling of keto-acid **104** with the homochiral 2°-alcohol *ent*-**26** gave ester *ent*-**105** (92%) and this underwent an RCM reaction to give neocosmosin A (*ent*-**92**) (67%), the structure of which was confirmed by single-crystal X-ray analysis.

During the course of these studies Das and co-workers reported[24] a distinctly different synthesis of compound *ent*-**94**.

Future Prospects/Conclusion

New RALs, including ones isolated from marine sources, that display intriguing biological properties continue to be reported.[25] Studies on the synthesis of such compounds have resulted, over the decades, in the identification of a raft of new methods for their construction and these have now provided chemists with the capacity to prepare new RALs in a predictable manner. As such, completions of total syntheses of RALs no longer elicit the excitement they once did.[26] Indeed, now synthetic studies usually just provide the means by which the assigned structures can be checked and additional material can be produced for the purposes of biological profiling/evaluation. Of course, the production of analogues is another important activity in this area, perhaps the most promising aspect of which would be the production of potentially more metabolically stable and bio-available macrolactam equivalents.[27]

Acknowledgements

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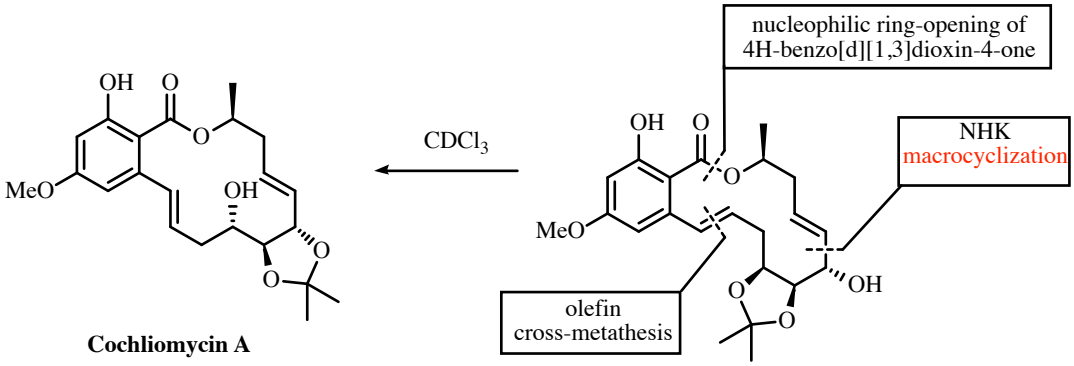
Highlights for TL-Digest Article entitled

Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

by

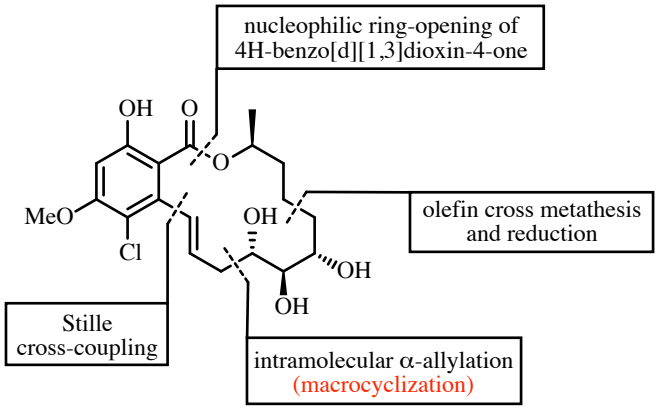
Martin G. Banwell,* Xiang Ma, Benoit Bolte, Yiwen Zhang and Michael Dlugosch

- All of the reported syntheses of the resorcylic acid lactones known as the cochliomycins are described.
- Novel methods for assembling the macrocyclic ring of the resorcyclic acid lactones are emphasized.
- The novel structural features and unique biological properties of the cochliomycins are delineated.



Cochliomycin A

Cochliomycin B



Cochliomycin C