Synthesis Mediated by Ring-Closing Metathesis – Applications in the Synthesis of Azasugars and Alkaloids

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The application of the ring-closing metathesis (RCM) reaction to the construction of a wide variety of nitrogen-containing ring systems is described. The examples include pyrrolizidine, indolizidine, and quinolizidine derivatives related to azasugars. A formal total synthesis of castanospermine (**5**) is presented. The utilisation of two RCM steps in the synthetic sequence leading to the multicyclic ABCDE nucleus **7** of the complex alkaloid manzamine A (**6**) is discussed.

1. Introduction

Carbon−carbon bond formation represents one of the important operations in organic synthesis. Olefin metathesis, or the transition-metal catalysed exchange of the alkylidene groups of two olefins, is now recognised as a useful practical tool for new (C=C) bond formation. This reaction has been historically used in polymer chemistry for ring-opening metathesis polymerisation (ROMP) reactions.[1] The development in recent years of several well-defined, highly active transition metal−alkylidene complexes (e.g. **1**−**3**), however, led to a plethora of applications in the area of carbocyclic and heterocyclic synthesis by a ring-closing metathesis (RCM) reaction. The scope and limitations of the RCM reaction has been reviewed extensively in recent years.[2]

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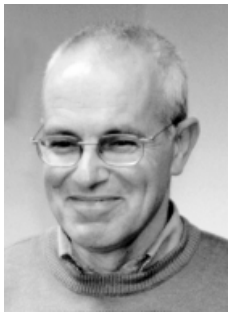
Hans Bieräugel (right, bottom) joined the group of Prof. U. K. Pandit in 1972. The focus of his recent work includes synthetic studies of natural products, such as manzamine A, as well as the development of inhibitors of enzymes essential for polynucleotide synthesis.



MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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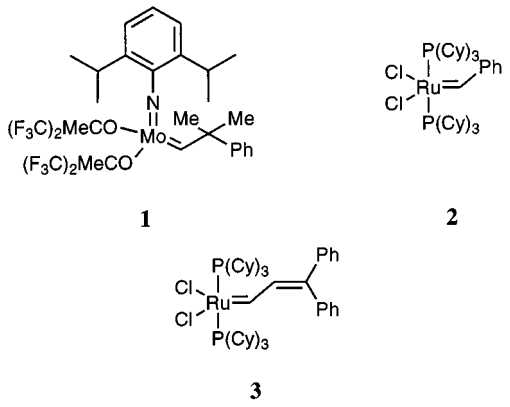


Figure 1. Metal−alkylidene complexes as RCM catalysts

The easy access, especially, to (alkylidene)metal catalysts **2**[3] and **3**,[4] combined with their relative stability and high functional-group compatibility, has greatly accelerated application of the RCM reaction in the field of organic synthesis. Thus, simple carbocyclic systems, like cyclopentene- and cyclohexene derivatives,[5] and heterocycles of different sizes containing both nitrogen[6] (as amines and amide functionalities) and oxygen atoms[7] (as cyclic ethers, enol ethers, and lactones) can today be readily obtained using the RCM strategy. More recently, the use of RCM reactions for the construction of annulated ring systems containing oxygen[8] and nitrogen,[9] including bicyclic β-lactams[10] has been described. Other valuable applications include the RCM reactions of polymer-bound dienes[11] and dienyne[12] systems. The potential to construct small, medium as well as large ring systems of various types, combined with the relatively high functional-group tolerance, makes the RCM reaction a versatile strategy in the area of natural product synthesis. In this context, several examples describing the total synthesis of naturally occurring macrolides,[13] and the solution and solid-phase synthesis of epothilone A and its analogues, have recently been described in the literature.[14] Finally, a de novo synthesis of a series of hydroxypyrrolizidines (azasugars) based on the RCM methodology, has been developed by Blechert et al.[15]

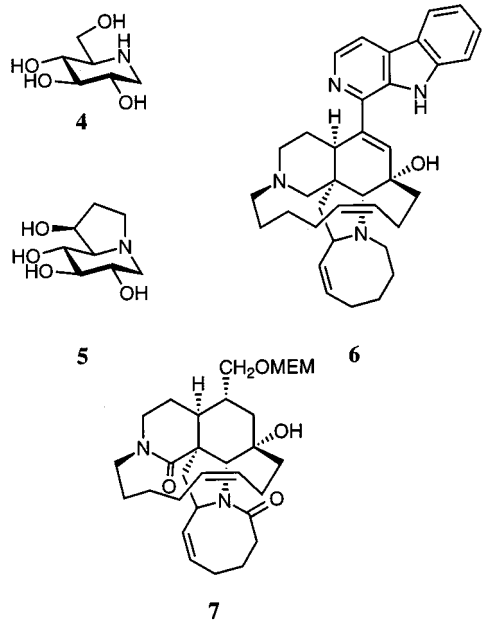


Figure 2. Synthetic targets castanospermine (**5**) and manzamine A (**6**)

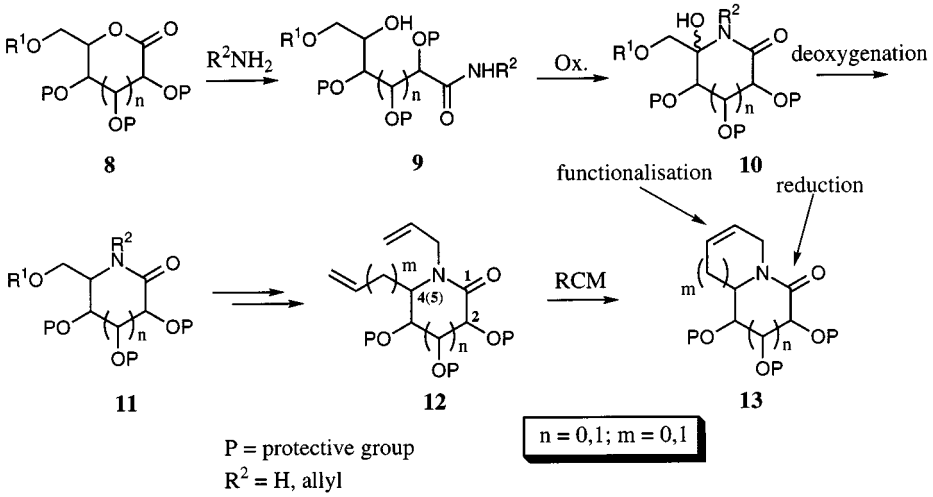
The present review focuses on our own work on the application of the RCM reaction in the construction of small, medium, and large nitrogen-containing rings. The first part of this paper describes an approach to the synthesis of bicyclic azasugars, based on the elaboration of aza-monosaccharide derivatives by the RCM reaction as a key step. A representative example is castanospermine (**5**), the bicyclic analogue of deoxynojirimycin (**4**). In the second part, the application of the RCM methodology in the assembly of the advanced intermediate (i.e. the pentacyclic nucleus **7**) for the complex marine alkaloid manzamine A (**6**) is discussed.

2. RCM-Mediated Synthesis of Bicyclic Azasugars

Azasugars are widely recognised as powerful tools for the study of the catalytic mechanism of enzymatic glycosyl transfer.[16] The replacement of the ring oxygen atom of a given carbohydrate by the nitrogen atom renders the compound physiologically stable, while still allowing it to be recognised by glycoside-processing enzymes. Thus, azasugars constitute a class of potential inhibitors of glycosidases and glycosyl transferases.[17] Interestingly, nature makes use of this feature and has evolved mimetics of virtually all monosaccharide building blocks. Representative examples which are pertinent to our study are deoxynojirimycin (**4**),[18] a glucopyranose mimetic (lacking the anomeric hydroxy function), and castanospermine (**5**)[19], the corresponding indolizidine system.

2.1 Strategy

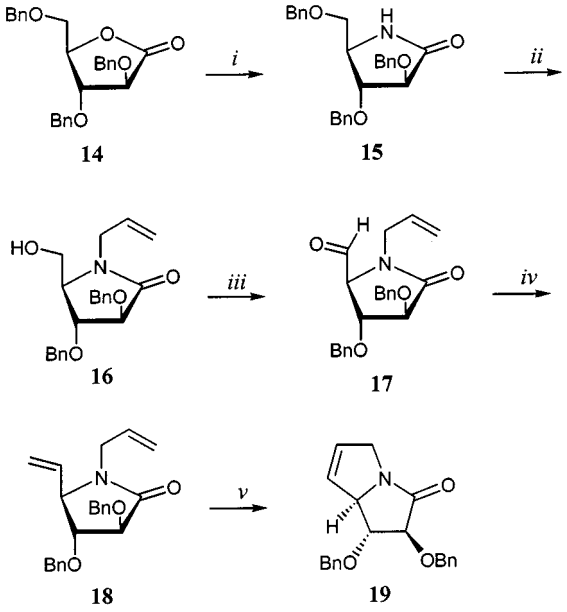
In the context of azasugar syntheses, a multitude of synthetic approaches to hydroxylated pyrrolidine, piperidine, pyrrolizidine and indolizidine derivatives have been reported.[20] Recently, the application of the RCM reaction in the synthesis of fused nitrogen-containing heterocycles, has been recognised. Thus, Martin et al.[9] prepared a series of annulated bicyclic lactams in which 5- to 8-membered rings were constructed by RCM on a γ- or δ-lactam core. Barret et al. have extended this approach to the construction of bicyclic β-lactam derivatives.[10] Furthermore, stemoamide, a tricyclic alkaloid with powerful insecticidal activity, has been synthesised utilising an enyne metathesis as a key step.[21] In all these approaches, it should be noted that annulated rings were prepared on an amide rather than an amine core. Although examples of successful RCM on amine functionality bearing precursors have been reported,[22] the efficiency of especially the ruthenium-based catalysts (**2** and **3**) appears to be diminished by the amine moiety.[23]



Scheme 1. RCM-mediated synthesis of bicyclic azasugars: general strategy

Our general strategy towards the construction of bicyclic azasugars on monosaccharide scaffolds is outlined in Scheme 1.

The approach rests on our previously reported[24] strategy for the stereoselective transformation of monosaccharide lactone building blocks into the corresponding lactams. According to this protocol, a furano- or pyranolactone **8** (n = 0 or 1, respectively), is treated with ammonia or allylamine to afford corresponding amides **9** (R^2 = H, allyl). Subsequent oxidation of **9**, followed by base-induced ring-closure furnishes hydroxylactams **10** (R^2 = H, allyl). Deoxygenation to the corresponding lactams **11** (R^2 = H, allyl), employing formic acid and sodium cyanoborohydride, is accomplished in high overall yield and often with high stereoselectivity. A closely related procedure has been developed independently by Vasella et al.[25] Functionalisation of **11**, i.e. *N*-allylation, and the introduction of a double bond at the 5- or 4-position affords the required RCM precursors (**12**). Following RCM, the double bond function in the products (**13**) can be further elaborated to give the corresponding bicyclic azasugars.



Scheme 2. Reagents and conditions: *i:* NH_3, MeOH, then Dess–Martin periodinane, then NH_3, MeOH, then $NaCNBH_3$, HCO_2H (4 steps, 57%); *ii:* allyl bromide, KOH (50% aq.)/CH_2Cl_2 (1:1, v/v), TBAI, then Ac_2O, $FeCl_3$, then NH_3, MeOH (3 steps, 70%); *iii:* Dess–Martin periodinane (85%); *iv:* $(Ph)_3PCH_3Br$, KHMDS, THF, −78°C (56%); *v:* **3** (0.5 equiv.), toluene, 50°C (66%)

2.2 Synthesis of Pyrrolizidine, Indolizidine, and Quinolizidine Systems

The synthesis of 2,3,5-tri-*O*-benzyl-D-arabino-1,4-lactam (**15**), from known lactone **14**, was easily accomplished[24] by the discussed procedure (Scheme 2). In order to explore the scope of the RCM-mediated synthesis of bicyclic azasugars from monocyclic sugar lactams, **15** was transformed into diene intermediate **18** by the sequence of reactions shown in Scheme 2.[26]

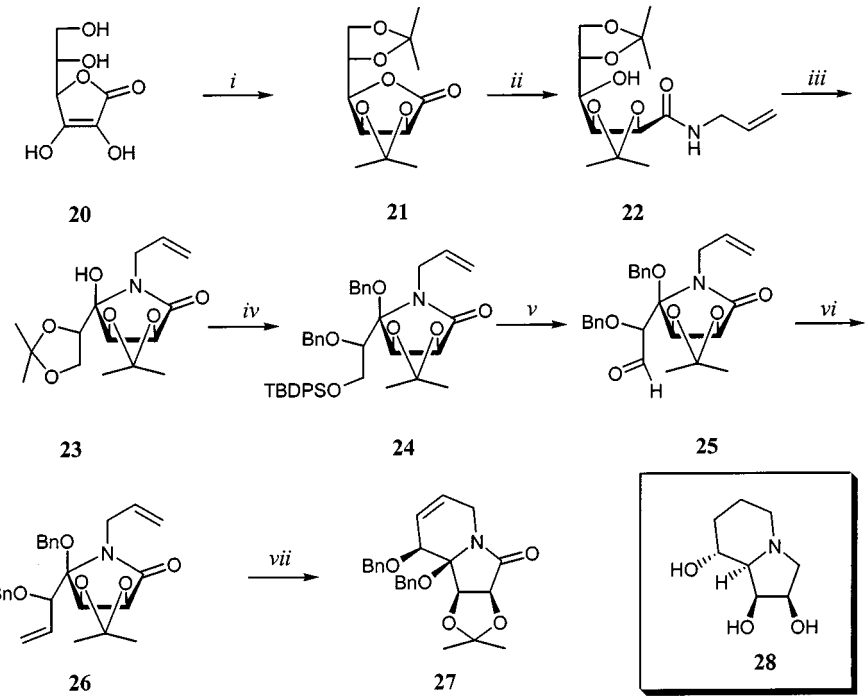
N-Allylation, employing two-phase conditions, followed by selective acetolysis of the primary benzyloxy group using ferric chloride and acetic acid[27] and subsequent hydrolysis of the resulting acetate afforded alcohol **16** in 70% overall yield (three steps). The Dess–Martin oxidation[28] of **16**, followed by Wittig olefination of the corresponding aldehyde **17**, afforded the desired diene **18** (48%). Subjection of **18** to the ensuing RCM reaction employing Ru catalyst **2** afforded the expected lactam **19** in 66% yield. However, the cyclisation step proved to be slow, neccessitating a prolonged reaction time and elevated temperature. Moreover, substantial quantities of the catalyst (0.5 mol equiv.) were required. The reluctant cyclisation to an otherwise facile 5-membered ring formation may be attributed to ring strain due to the presence of the amide carbonyl group in the lactam template. In this context, it should be noted that Blechert et al. reported a failure of the RCM-mediated generation

of a 5-membered ring on a cyclic carbamate template.[15] In the next example, the formation of a six-membered ring on a similar template is discussed (Scheme 3).

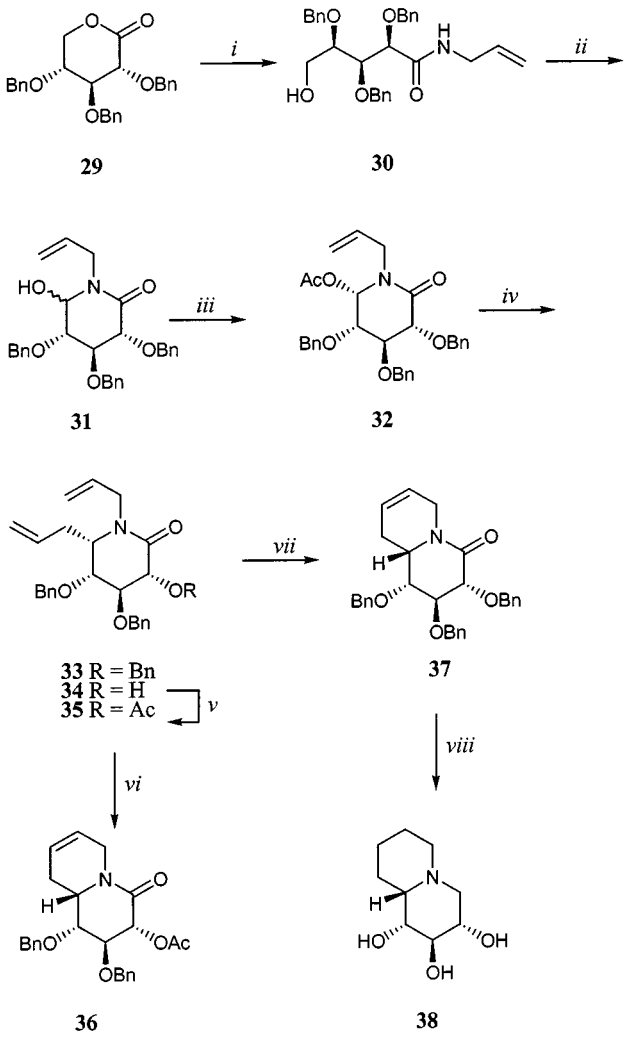
As the stereoselective hydrogenation of L-ascorbic acid **20** to L-gulonolactone has been previously described,[29] it appeared to be an attractive starting material which could be carried through the developed sequence to bicyclic azasugars. Accordingly, hydrogenation of **20**, followed by diol protection, afforded lactone **21** in excellent yield. Aminolysis of **21** employing allylamine in methanol afforded amide **22**, which was subsequently oxidised by using pyridinium dichromate (PDC) in refluxing chloroform to give hydroxylactam **23** as a single stereoisomer (80%). The stereochemistry of **23** was firmly established by NOE difference experiments. At this stage no complication was envisaged in the reduction of the hydroxylactam to the corresponding lactam. However, the hydroxy group in **23** proved to be very unreactive under standard conditions (formic acid/sodium cyanotrihydroborate[24] or triethylsilane/BF_3−ether[25]). Under these reaction conditions, either hydrolysis or reduction of the 5,6-di-*O*-isopropylidene moiety was responsible for the observed products. Consequently, it was decided to modify the strategy and first introduce the required alkene moiety. This required the selective deprotection of C-6 in **23**. The latter was accomplished by protective-group manipulations; viz. selective hydrolysis of the 5,6-di-*O*-isopropylidene, followed by silylation of the primary hydroxy group and subsequent benzylation of the remaining hydroxy function. Formation of benyloxylactam **24** proceeded in 40% yield (3 steps). Unmasking of the primary alcohol (TBAF, THF), followed by Dess−Martin oxidation gave aldehyde **25**, which was subsequently olefinated (Ph_3PCH_3Br, BuLi) to give diene **26** (50%, three steps). Diene **26**, in turn, was cyclised employing Ru catalyst **2** in toluene at 50°C to afford bicyclic benzyloxylactam **27** in 80% yield. This highly functionalised lactam is expected to be a useful intermediate for a future synthesis of swainsonine **28** and its analogues.

To illustrate the versatility of the strategy, attention was then directed to the synthesis of a quinolizidine system based on perbenzylated xylopyranolactone **29**. The latter is easily accessible from xylose in a known[30] three-step procedure. Treatment with allylamine, followed by Dess−Martin oxidation and base-catalysed ring-closure, led to the expected hydroxylactam **31** in 75% yield (Scheme 4).

The second alkene moiety was now introduced by transformation of **31** into the corresponding acetoxylactam **32**, followed by treatment with allyltrimethylsilane/BF_3−ether. Under these conditions, partial debenzylation of the 2-benzyloxy group took place, resulting in a mixture of **33** and **34** (1:1; 66%). This unexpected side-reaction is thought to result from complexation of the Lewis acid to the oxygen atom in 2-position, followed by attack of the nucleophile at the benzylic position. The acetylation of **34** to **35** facilitated the determination of its structure. The formation of the L-*ido* addition products is in accordance with the expected attack of the nucleophile on the α-face of the in situ generated *N*-acyliminium ion.[31] Dienes **33** and **35** were now submitted to the crucial RCM reaction. Cyclisation of **35** with Ru catalyst **2** resulted in the formation of quinolizidinone **36** in excellent yield. Similarly, the perbenzylated analogue **37** was obtained from **33**, employing Ru catalyst **3**.



Scheme 3. Reagents and conditions: *i:* H_2, Pd/C, then 2,2-dimethoxypropane, acetone, TSA (95%); *ii:* allylamine, MeOH (95%); *iii:* PDC, pyridinium trifluoroacetic acid (cat.), $CHCl_3$, reflux (80%); *iv:* AcOH/H_2O (5:1), then TBDPSCl, pyridine, then NaH, BnBr, DMF (3 steps, 40%); *v:* TBAF, THF, then Dess−Martin periodinane (84%); *vi:* $(Ph)_3PCH_3Br$, BuLi, THF, −78°C (60%); *vii:* **3** (5 mol-%), toluene, 50°C (80%)

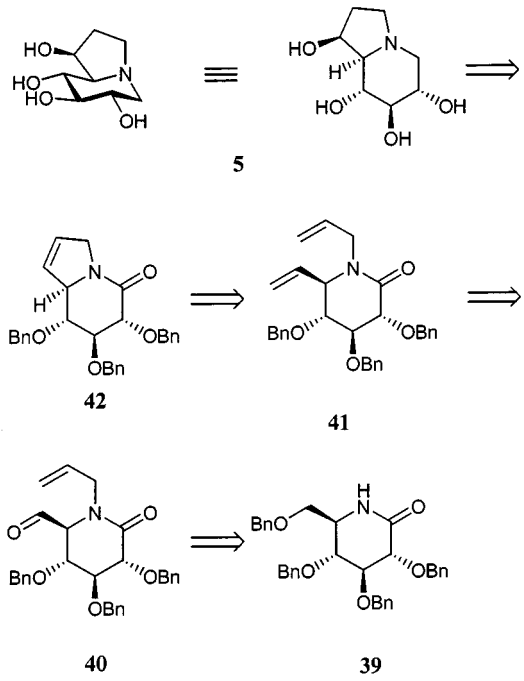


Scheme 4. Reagents and conditions: *i:* allylamine, MeOH (98%); *ii:* Dess−Martin periodinane, then NH_3, MeOH (77%); *iii:* Ac_2O, pyridine, DMAP (91%); *iv:* allyltrimethylsilane, $BF_3{-}OEt_2$ (33% **33**, 33% **34**); *v:* Ac_2O, pyridine, DMAP (93%); *vi:* **2** (2.5 mol-%), CH_2Cl_2 (95%); *vii:* **3** (2.5 mol-%), CH_2Cl_2 (74%); *viii:* $LiAlH_4$, THF, then H_2, Pd/C, HCl (57%)

Finally, reduction of the amide function in **37** ($LiAlH_4$, THF) followed by hydrogenation of the double bond and removal of the benzyl protecting groups, led to the formation of quinolizidine **38** in 57% yield (two steps). To the best of our knowledge, this compound is the first example of a hydroxylated quinolizidine with this substitution pattern.[32]

2.3 Formal Synthesis of Castanospermine

In this section, the application of the RCM strategy to the formal synthesis of castanospermine (**5**) (Scheme 5) is discussed.[33] Using the protocol (Scheme 1) for the general synthesis of sugar lactams, the intermediate 2,3,4,6-tetra-*O*-benzyl-D-glucono-δ-lactam (**39**) was prepared on a multigram scale.[24][25] We envisaged that the total synthesis of castanospermine (**5**) could now be accomplished through the construction of a second ring on the gluconolactam template, as outlined in Scheme 5.

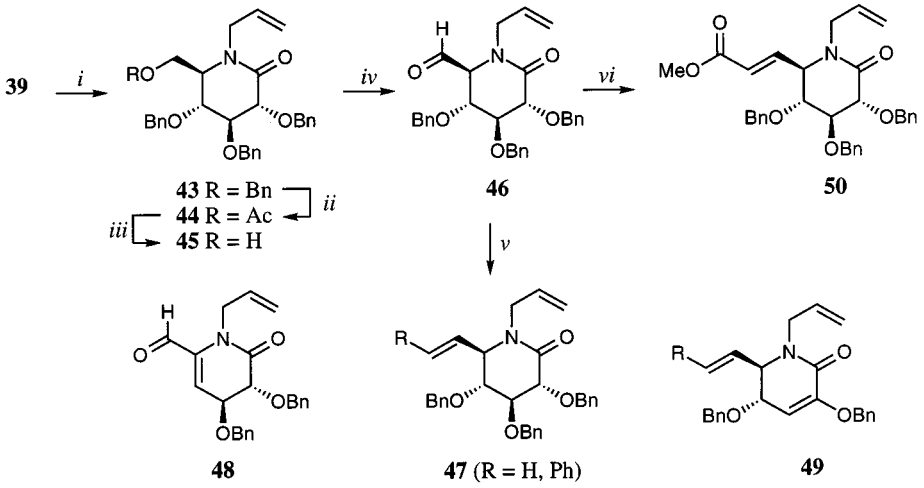


Scheme 5. Castanospermine − retrosynthetic analysis

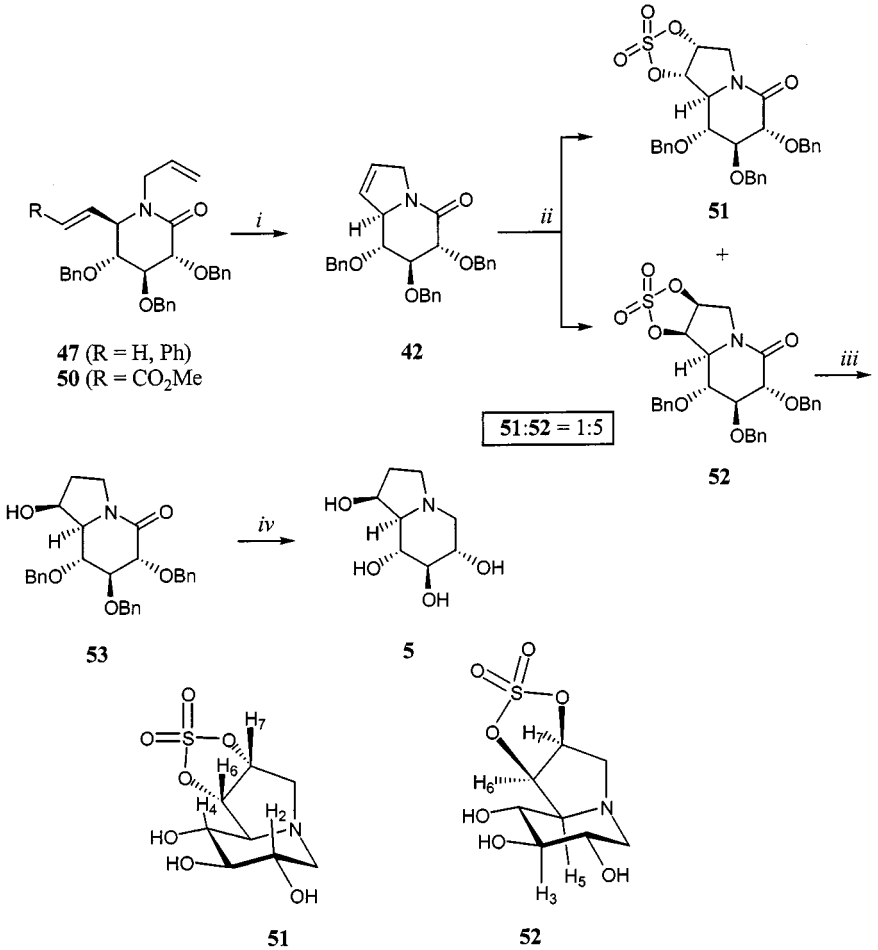
According to Scheme 6, *N*-allylation of lactam **39** was accomplished with allyl bromide using two-phase conditions and employing tetrabutylammonium iodide as the phase-transfer catalyst. Treatment of the resulting tertiary lactam **43** with ferric chloride in acetic anhydride resulted in the selective acetolysis of the primary benzyloxy group, to give acetate **44**. Compound **44** was subjected to hydrolysis in methanolic ammonia whereupon it was selectively deprotected to **45** which was oxidised to key intermediate **46** employing the Dess−Martin periodinane reagent (72% yield, 4 steps based on **39**). The introduction of the second alkylidene moiety at this stage was first attempted by a standard Wittig protocol. However, treatment of **46** with $Ph_3P^+CH_3Br^-$ in the presence of *n*-butyllithium gave the desired diene **47** (R = H) in very low yield (10%), due to formation of several elimination products (i.e. **48**, **49**). The formation of these side products under the basic conditions may be attributed to the acidity of the protons adjacent to the carbonyl moieties in **46**, i.e. at C-2 and C-5. In an attempt to partially "soften" the ylide, the phenyl-substituted variant was treated with **46**. Athough the yield of **47** (R = Ph) was higher than that observed for **47** (R = H), nevertheless, no more than 18% of the Wittig product could be isolated. Again, the reaction was thwarted by concomittant formation of several elimination products. In an alternative approach, utilisation of a Peterson olefination reaction was attempted. However, once again, only elimination products were observed. The application of non-basic titanium-based olefination methods, such as the Tebbe olefination[34] (yield 25−45%) or the $CH_2I_2{-}TiCl_4{-}Zn$ system[35] (yield < 10%) afforded diene **47** (R = H), but again the yields were unsat-

isfactory. At this point, we turned our attention to a Wittig reaction employing a stabilised ylide. Thus, condensation of **46** with methyl (triphenylphosphoranylidene)acetate afforded compound **50** in excellent yield. Compound **50** could thereafter be synthesised in reasonable quantities, allowing the study of the key RCM reaction (Scheme 7).

All the three diolefins described above were subjected to an RCM reaction employing Ru catalyst **2**. The dienes **47**



Scheme 6. Reagents and conditions: *i:* allyl bromide, KOH (50% aq.)/CH_2Cl_2 (1:1, v/v), TBAI (87%); *ii:* Ac_2O, $FeCl_3$; *iii:* NH_3, MeOH (2 steps, 88%); *iv:* Dess−Martin periodinane (93%); *v:* $(Ph)_3PCH_3Br$, BuLi, THF, −78°C [10% **47** (R = H), 19% **48** (R = H), 21% **49** (R = H)] or $(Ph)_3PCH_2PhBr$, BuLi, THF, −78°C [18% **47** (R = Ph), 20% **49** (R = Ph)]; *vi:* $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (84%)



Scheme 7. Reagents and conditions: *i:* from **47** (R = H): **3** (3 mol-%), toluene, room temp. (80%), from **47** (R = Ph): **3** 10 mol-%, toluene, room temp. (90%), from **50**: 3 (8 mol-%, toluene, reflux (70%); *ii:* OsO_4, NMO, then $SOCl_2$, Et_3N, then $NaIO_4$, $RuCl_3$ (3 steps, 43% **52**, 8% **51**); *iii:* $NaBH_4$, *N*,*N*-dimethylacetamide, then H_2SO_4 (98%); *iv:* BH_3−DMS, then H_2, Pd/C[39]

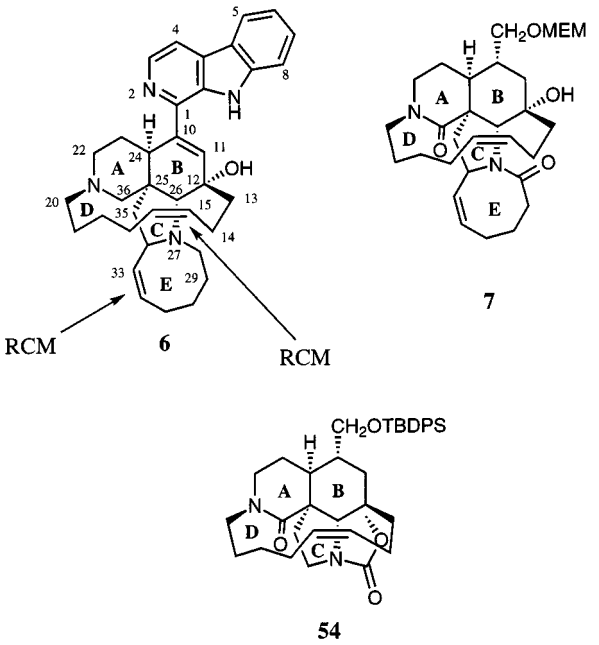
(R = H, Ph) both cyclised smoothly to give the bicyclic lactam (80%). As anticipated, the cyclisation of **50** to **42** was a much more difficult process. At room temperature, virtually no reaction occurred, aside from a slow decomposition of the catalyst over 24 h. However, in toluene at 110°C, cyclisation proceeded within 16 h using 8 mol-% of the catalyst. The yield in the last example, i.e. conversion of **50** into **42**, was considerably lower than that observed for the other two diene precursors. However, considering the difficulties in obtaining dienes **47**, the route via **50** was preferred. Furthermore, this example of RCM of an intermediate bearing an α,β-unsaturated ester (to form methyl acrylate as the side-product) is to the best of our knowledge unprecedented.

The double bond was further functionalised en route to a formal synthesis of castanospermine (**5**) (Scheme 7). At first, we considered a sequence by the formation of an epoxide and selective ring opening to the desired alcohol. However, reaction with either dimethyldioxirane or with *m*CPBA was unsuccessful. Consequently, in an alternative approach, the double bond was oxidised employing osmium tetroxide with *N*-methylmorpholine *N*-oxide as the cooxidant,[36] to afford an unseparable mixture of the expected diols. This mixture was converted into cyclic sulphates **52** and **51** (5:1) via the corresponding sulphites according to a known procedure.[37] Separation of the mixture at this stage provided the major product. i.e. the cyclic sulphate **52** in an overall yield of 43% (three steps). The relative configuration of the cyclic sulphates **51** and **52** has been firmly established by NOE experiments (Scheme 7). Irradiation of 5-H in **52** gave a positive effect on 6-H and vice versa, attesting to the fact that these protons lie on the same side of the bicyclic framework. From analogous experiments performed on the minor isomer **51**, the proximity of 4-H and 6-H was established. In this case, no NOE interaction between 5-H and 6-H was observed.

Finally, the cyclic sulphate **52** was treated with sodium tetrahydroborate in *N*,*N*-dimethylacetamide[38] to yield a monosulphate which, upon hydrolysis, gave lactam **53** as the single regioisomer. In the reduction step, the product resulting from attack on the sterically less congested site is formed exclusively. The spectroscopic data for **53** are in full agreement with those published in the literature.[39] Furthermore, the transformation of **53** to castanospermine (**5**) in a two-step sequence (reduction of the lactam to the indolizidine followed by deprotection) has already been accomplished by Miller et al.[39] Thus, the presented work represents a formal synthesis of castanospermine (**5**) form tetrabenzylgluconolactam **39** in 11 steps, with an overall yield of 18%.

3. Strategy for the Synthesis of Manzamine A

Manzamine A (**6**) is a challenging target in view of its antileukemic and antibacterial activities and in particular owing to its unique structure.[40] It consists of a pentacyclic heterocyclic nucleus onto which a β-carboline ring system is attached as a pendant substituent. Due to aforementioned reasons, manzamine A has attracted considerable attention from synthetic organic chemists.[41] We recognised that the 13-membered D-ring, as well as the 8-membered E-ring, both possess an internal double bond, and could therefore be accessible by RCM reaction of suitable diene precursors. To illustrate this point, initially the model ABCD system **54** was prepared.[42] In a subsequent study, the first reported synthesis of the key ABCDE core intermediate **7** was achieved.[43]



6 **7** **54**

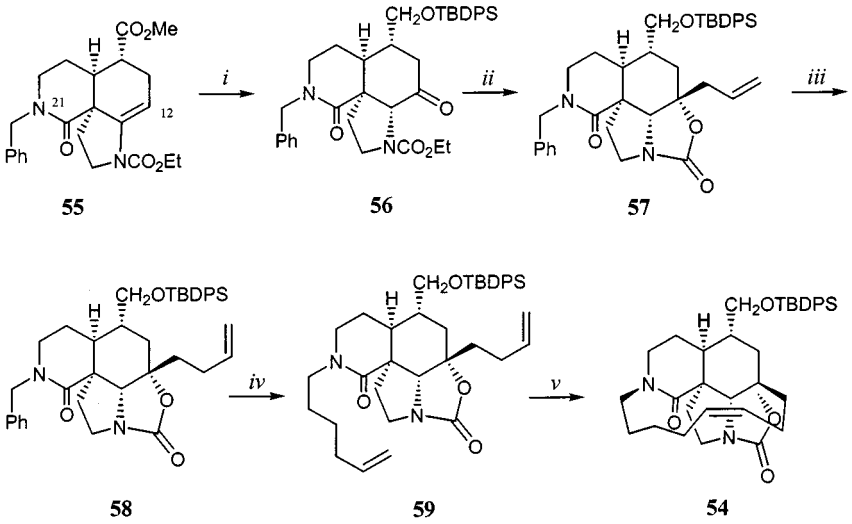
Figure 3. Manzamine A − retrosynthetic analysis

3.1 Synthesis of a 13-Membered-Ring-Bearing ABCD System

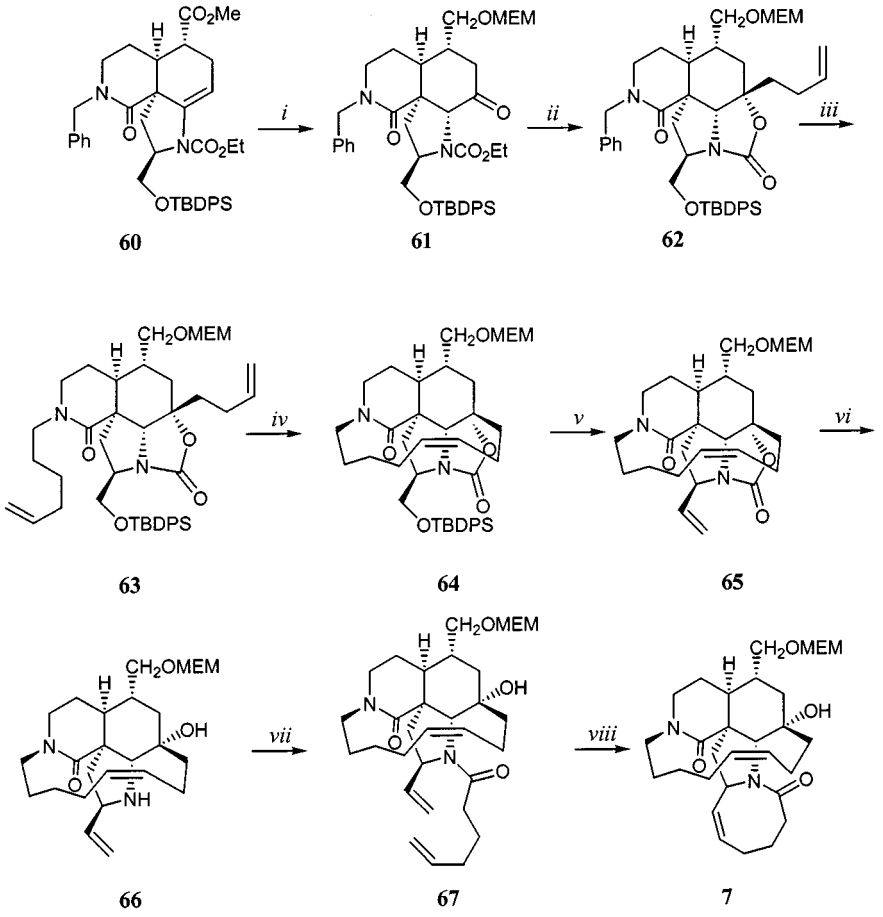
The construction of the ABCD system **54** is outlined in Scheme 8 and commences with the tricyclic precursor **55**. A synthetic strategy to racemic **55**, as well as its homochiral analogues (based on an intramolecular Diels−Alder reaction) has been previously reported from our laboratory.[44]

It was envisaged that the introduction of the required alkene substituent at C-12 (manzamine numbering) could be achieved through the addition of an appropriate organometallic reagent to a ketone function. To this end, the C-12 ester functionality was reduced, and the resulting alcohol protected as the *tert*-butyldiphenylsilyl ether. Transformation to the C-10 ketone function was next achieved by the following two-step sequence: (i) oxidation of the double bond employing osmium tetroxide; (ii) acid-catalysed dehydration of the resulting diol to the dion **56** (45%, 4 steps). At this stage, the introduction of the required homoallylic function at C-12 was investigated. Reaction of **56** with homoallyl magnesium chloride did not result in addition to the ketone. The same result was obtained when a variety of other magnesium, lithium or cerium reagents were added to the ketone, apparently due to steric hindrance. Utilisation

of a more reactive allyl Grignard reagent[45], however, resulted in addition (60%) to the ketone to give a single product, involving top-face addition from the sterically less hindered side. The resulting tertiary amine was protected by its transformation to the cyclic carbamate **57** by treatment with sodium hydride in THF (93%). Carbon-extension of the allyl derivative to the desired homoallyl derivative was now achieved by the following three-step sequence: hydrobo-



Scheme 8. Reagents and conditions: *i:* $LiBH_4$, then TBDPSCl, imidazole, DMF, then OsO_4, pyridine, then H^+ (4 steps, 45%); *ii:* allylMgCl, THF, then NaH, THF (56%); *iii:* 9-BBN, H_2O_2, then Dess−Martin periodinane, then $(Ph)_3PCH_3Br$, BuLi, THF, −78°C (3 steps, 48%); *iv:* Li/NH_3, then Bn_2O, then $I[CH_2]_4CH{=}CH_2$, KOH, DMSO (77%); *v:* **3** (20 mol-%), toluene, room temp., 5 d (30%)



Scheme 9. Reagents and conditions: *i:* $LiBH_4$, THF, then MEMCl, NaH, DMF, then OsO_4, pyridine, then H^+; *ii:* homoallylMgBr, THF, then NaH, THF; *iii:* Li/NH_3, then Bn_2O, then $I[CH_2]_4CH{=}CH_2$, KOH, DMSO; *iv:* **3** (10 mol-%), toluene, room temp., 18 h (55%); *v:* TBAF, THF, then Dess−Martin periodinane, then then $(Ph)_3PCH_3Br$, BuLi, THF, −78°C; *vi:* 40% KOH/MeOH; *vii:* $CH_2CH{=}CH[CH_2]_3CO_{2\ H}$, EDC, CH_2Cl_2; *viii:* **3** (15 mol-%), toluene, 50°C, 5%)

ration of the double bond, oxidation of the resulting primary hydroxy group to the aldehyde and Wittig olefination. Compound **58** was formed in 48% overall yield. In order to attach the second olefinic side chain, the *N*-benzyl-protecting group was removed with lithium in ammonia (dibenzyl ether was added in order to avoid accompanying Birch reduction of the phenyl substituents at the *tert*-butyldiphenylsilyl group[46]). The resulting secondary amide group was alkylated with 6-iodohex-1-ene in DMSO in the presence of excess KOH (**59**, 77%, two steps). The ensuing RCM reaction employing Ru catalyst **2** (20 mol-%) afforded, after stirring at room temperature for 5 d, the ABCD system **54**, as a single diastereomer, in 30% yield.[42]

3.2 Assembly of the ABCDE System

Encouraged by the successful construction of a 13-membered ring, we set out to construct the complex ABCDE system **7** (Scheme 9). To this end, the chiral tricyclic precursor **60** was converted into ABCD system **64** by essentially the same sequence of reactions as described previously.

Reduction of the C-10 ester afforded the corresponding primary alcohol, which was now protected as the methoxyethoxymethyl ether. Conversion into C-12 ketone **61** could be achieved according to the above-described two-step procedure. At this stage the addition of the homoallyl Grignard reagent led, once again, to selective addition from the top side of the molecule. However, in contrast to the previously described allylation step, homoallylation resulted directly in the formation of cyclic carbamate **62**. The reaction is presumably successful owing to the smaller protecting group at C-1. The RCM precursor **63** was synthesised according to the earlier described 2-step sequence (Li/NH_3, alkylation at N-22). RCM of **63** proceeded smoothly to afford crystalline **64**, representing the ABCD system of manzamine A, in 55% yield. With the success of the RCM reaction in the elaboration of ring D, we embarked on the construction of the azocine ring E on compound **64**, by the same strategy. At this point, it is of interest to note that a successful conversion of a tricyclic ABC intermediate into a corresponding ABCE system by using molybdenum catalyst **1** has been reported by Martin et al.[47] In order to achieve the desired transformation in the case of **64**, the hydroxymethyl function at C-34 was deprotected and oxidised to give the corresponding aldehyde. Introduction of the first double bond was subsequently achieved by Wittig olefination (**65**). The cyclic carbamate system in **65** was hydrolysed employing 40% KOH in methanol, to give the tetracyclic pyrrolidine intermediate **66**. Acylation of the pyrrolidine nitrogen atom with hex-5-enoic acid in the presence of EDC resulted in diene **67** which was subjected to the RCM reaction employing Ru catalyst **3**. By this sequence, the ABCDE system **7** was obtained, albeit in low yield (5%).[43] At the time of the completion of this sequence, this constituted the first example of a synthesis of the ABCDE moiety of manzamine A. It should be noted that, very recently, Winkler et al. have completed a total synthesis of manzamine A.[48]

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