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Some recent applications of olefin metathesis in organic synthesis: A review

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Abstract

A review is given of a selection of papers published in the past year in this rapidly expanding field. Such papers may be divided into four groups: (i) those in which ring-closing metathesis (RCM) has been used as a key step in the total synthesis of a natural product: (*R*)-(+)-lasiodiplodin, dactylol, (−)-stemoamide, and epothilone A; (ii) those in which RCM has been used to make a sub-unit of a natural product: the marine toxins brevetoxin B, brevetoxin A, and maitotoxin; (iii) those in which RCM has been used to make compounds of known biological activity: fluvirucin B_1 (Sch 38516); (iv) those in which metathesis reactions have been used to make compounds of potential synthetic importance: crown ethers, aza sugars (polyhydroxylated pyrrolidines), β-lactams, chromenes, and aminoacids. The catalysts used have been one of the following four metal carbene complexes: the Schrock catalyst $Mo(=CHCMe_2Ph)(=NC_6H_3\text{-}2,6\text{-}i\text{-}Pr_2)[OCMe(CF_3)_2]_2$; the Grubbs catalysts $Ru(=CHCH=CPh_2)Cl_2(PCy_3)_2$ and $Ru(=CHPh)Cl_2(PCy_3)_2$, where Cy = cyclohexyl; and the Tebbe reagent which behaves as $Ti(=CH_2)Cp_2$, where Cp = cyclopentadienyl. In this paper these are denoted by Mo-1, Ru-1, Ru-2, and Ti-1, respectively. Ti-1 is especially useful for effecting RCM by the carbonyl–olefination reaction, while the RCM of enynes, catalyzed by Ru-2, is another valuable metathesis reaction.

1. Introduction

The last few years have seen an explosion of applications of the olefin metathesis reaction in organic synthesis, particularly using ring-closing metathesis (RCM). Some of these have been summarized in a recent book [1]. In this paper we review some further applications, published in the period July 1996 to May 1997.

2. General considerations

The burgeoning number of applications has been stimulated by the commercial availability of the very effective molybdenum and ruthenium carbene complex catalysts developed by Schrock and

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Grubbs respectively. The Tebbe reagent is also useful for bringing about the related carbonyl–olefination reaction.

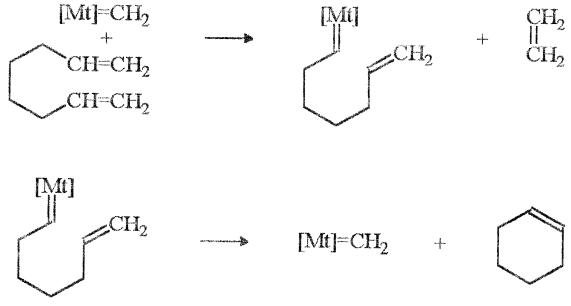
Mo-1	$Mo(=CHCMe_2Ph)(=NC_6H_3\text{-}i\text{-}Pr_2\text{-}2,6)[OCMe(CF_3)_2]_2$	**Schrock**
Mo-2	$Mo(=CHCMe_2Ph)(=NC_6H_3\text{-}i\text{-}Pr_2\text{-}2,6)[OCMe_3]_2$	**Schrock**
Ru-1	$Ru(=CHCHCPh_2)Cl_2(PCy_3)_2$ (Cy = cyclohexyl)	**Grubbs**
Ru-2	$Ru(=CHPh)Cl_2(PCy_3)_2$	**Grubbs**
Ti-1	$Cp_2Ti(Cl)(AlMe_2)CH_2$ which behaves as $Ti(=CH_2)Cp_2$ (Cp = cyclopentadienyl)	**Tebbe**

Mo-1, Mo-2 and Ru-2 are available from Strem Chemicals (May 1997). The amount of catalyst required depends on the rate of the RCM reaction relative to that of any side reactions leading to destruction of the catalyst. Less than 10% of the substrate concentration is generally sufficient, but sometimes it is necessary to increase this to 25%.

The RCM of a diene (or of an enyne) involves two alternating types of propagation reaction as illustrated in Scheme 1 for the simple case of the reaction of octa-1,7-diene. An *inter*molecular metathesis reaction (1) is followed by an *intra*molecular metathesis reaction (2). The ease of occurrence of both these reactions and the stereoselectivity of the latter varies with the catalyst; the best for a given RCM must be found by trial and error.

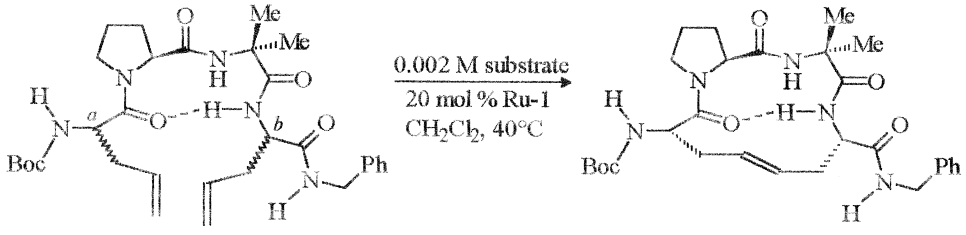
The substrate concentration is an important factor in the success of any RCM reaction. Dilute solution (0.01 M) favours the intramolecular reaction of the metal carbene complex leading to RCM, and disfavours the competing intermolecular reaction leading to dimer, trimer and higher polymers by metathesis condensation. Dilute solution also disfavours the secondary ROMP of the cyclic product of the RCM reaction because such reactions only proceed to a significant extent above a critical concentration of the cyclic compound [2]. In a homologous series of reactions this critical concentration becomes progressively lower as the ring size of the product is increased. In the ring-opening polymerization of cycloocta-1,5-diene it is possible to detect up to 52-membered rings in the cyclic products [3]. It is therefore not out of the question to bring about closure of quite large rings by RCM as exemplified below for the formation of a 26-membered crown ether.

Rotation about the bonds separating the two multiple bonds undergoing RCM is restricted by a number of factors. Apart from the normal rotational barriers around single bonds there may be



Scheme 1. Mechanism of ring-closing metathesis (Mt = metal center).

multiple bonds, or the bonds may form part of one or more ring systems; and there may be hydrogen bonds which further restrict the available conformations. These restraints can have an important bearing on the probability of occurrence of RCM, sometimes favouring RCM by bringing the reacting Mt=C and C=C bonds into closer proximity, sometimes disfavouring RCM by holding the Mt=C and C=C bonds further apart, especially for the formation of smaller rings. If there are chiral centres between the two reacting multiple bonds then the RCM of one diastereomer may be favoured over the others. A notable example of this is shown in the reaction below. There are chiral centres at *a* and *b* in the substrate (**1**) but only one of the four diastereomers undergoes ring closure in the presence of Ru-1 [4].



(1) (mixture of 4 diastereomers) (*S,S,S*)-(**2**) formed from one diastereomer

(3)

In what follows, for each synthesis, we shall indicate (i) the starting materials for the preparation of the diene or other substrate, (ii) the metathesis stage, enclosed by a box, and (iii) the overall yield.

3. Synthesis of some natural products

*3.1. (R)-Lasiodiplodin (**3**)*

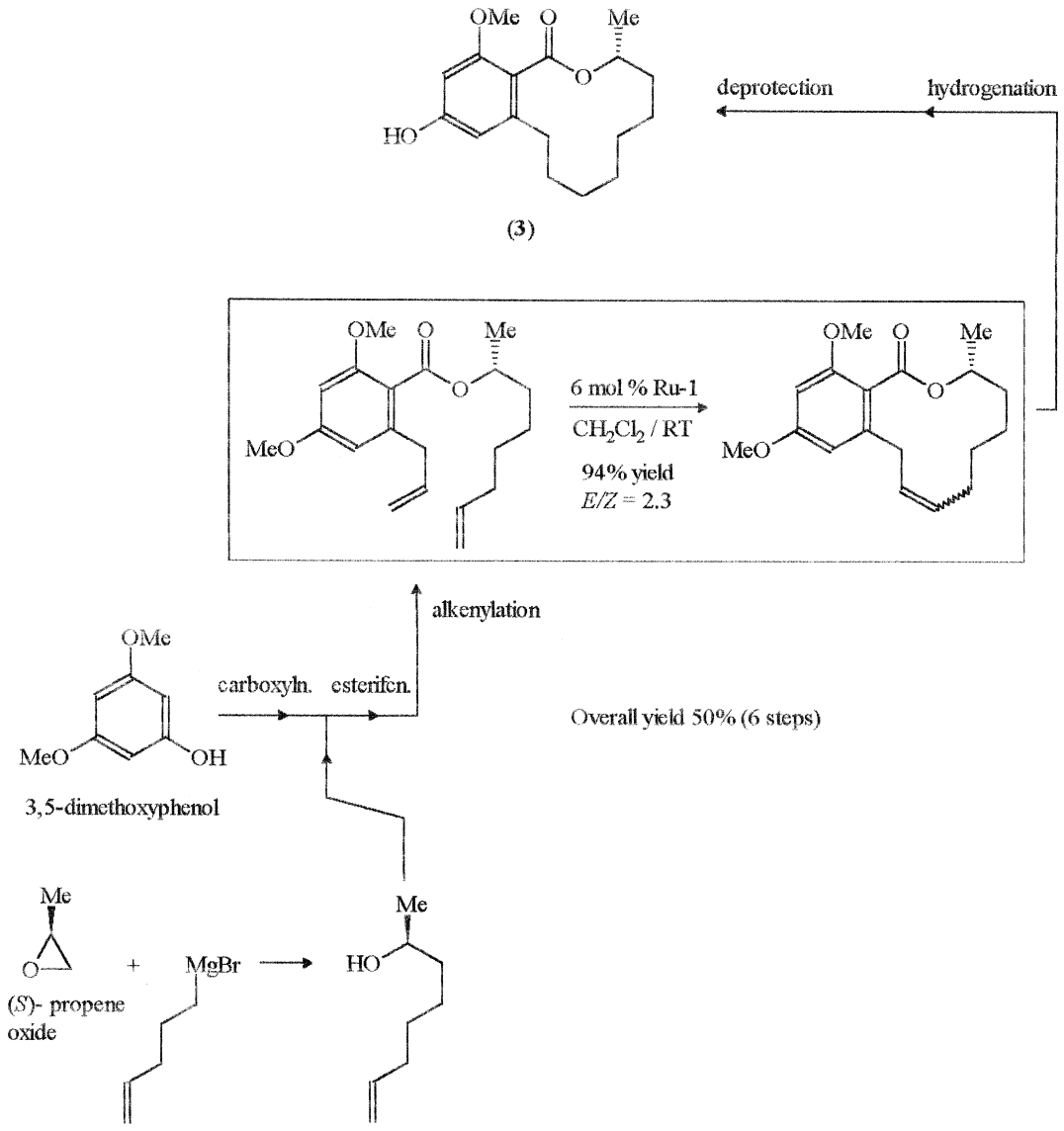
This compound can be isolated from a culture broth of the fungus *Botrysdiplodia theobromae* (formerly *Lasiodiplodia theobromae*) and exhibits plant growth regulation properties. A method of synthesis employing RCM is shown in Scheme 2 [5].

The formation of the 12-membered ring in the RCM reaction is nearly quantitative. The chiral centre bearing the methyl group derives from that in the starting compound (*S*)-propene oxide. The first alkenyl group required in the substrate is introduced at the aromatic 2-position by an esterification reaction. The second alkenyl group is introduced by conversion of OH to OSO_2CF_3 followed by a catalyzed reaction with allyltributylstannane.

*3.2. (±)-Dactylol (**4**)*

This is a cyclooctenoid sesquiterpene first isolated in 1978 from the mollusc *Aplysia dactylomela* (Carribean sea hare) and from the seaweed *Laurencia poitei* on which it probably feeds. A method of synthesis employing RCM is shown in Scheme 3 [6].

Efficient formation of the 8-membered ring is achieved using Mo-1 as catalyst. The hydroxyl group must be protected to prevent the destruction of the catalyst. The first alkenyl group required in the substrate is introduced at the 2-position in cyclopenten-2-one by reacting it with the organocopper reagent formed from $MeLi/CuI/Bu_3P$ at low temperature followed by addition of 2,2-dimethylpenten-4-al to trap the intermediate enolate. The second alkenyl group is introduced at the 3-position



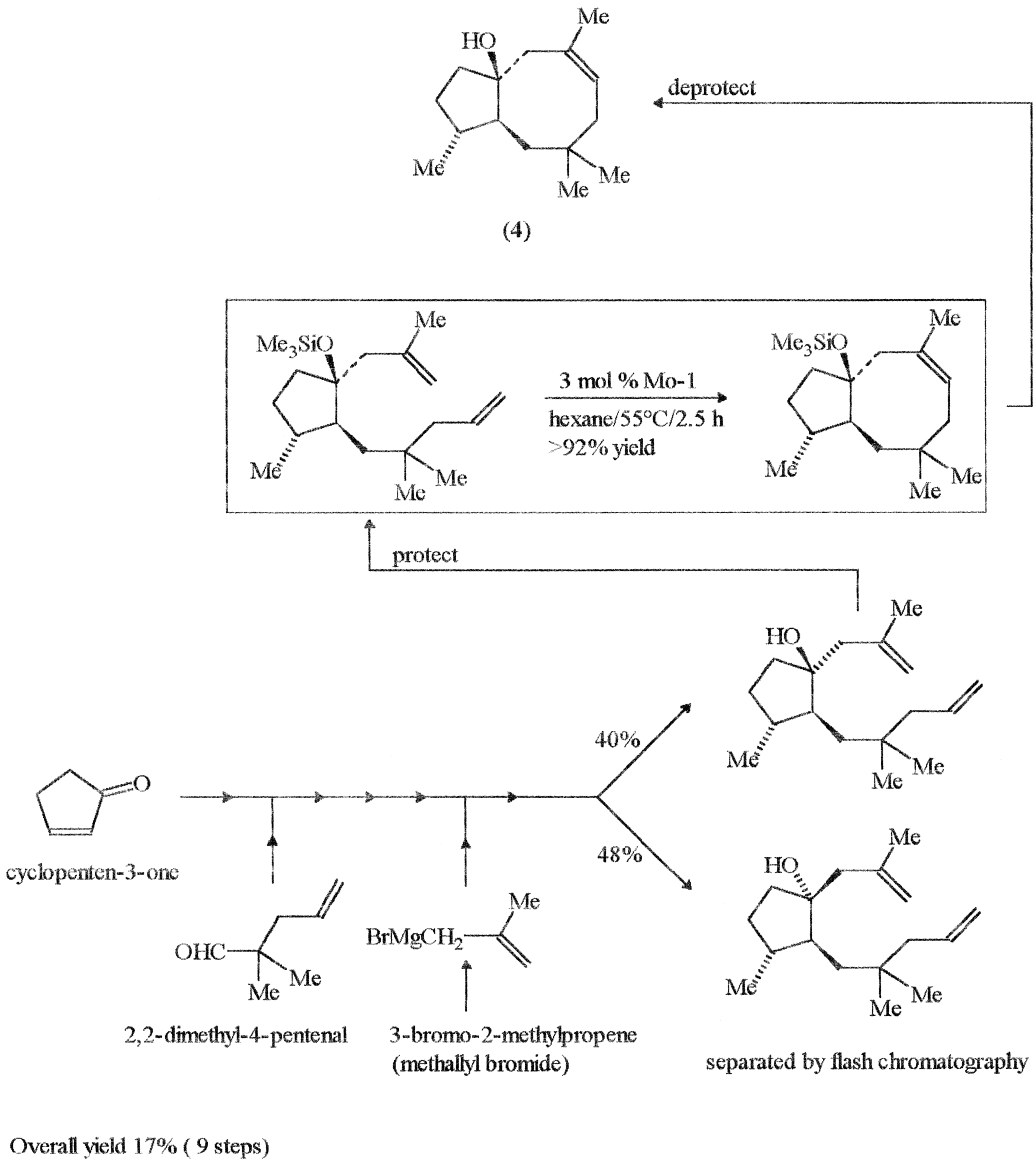
Scheme 2. Synthesis of (*R*)-(+)-lasiodiplodin (**3**).

by reaction of the carbonyl group at −78°C with the cerium analogue of the Grignard reagent derived from methallyl bromide. Previous syntheses are surpassed in terms of efficiency and practicability.

*3.3. (−)-Stemoamide (**5**)*

This polycyclic alkaloid, isolated from the roots and rhizomes of *Stemonaceous* plants, and a powerful insecticide, can be synthesized according to Scheme 4 [7].

The formation of the 7-membered ring is accomplished in good yield by the RCM of an enyne, catalyzed by Ru-2. The third ring is formed via a bromolactonization reaction in the final stages of the synthesis. The alkenyl group required in the substrate is introduced by reaction of 5-bromopent-1-ene

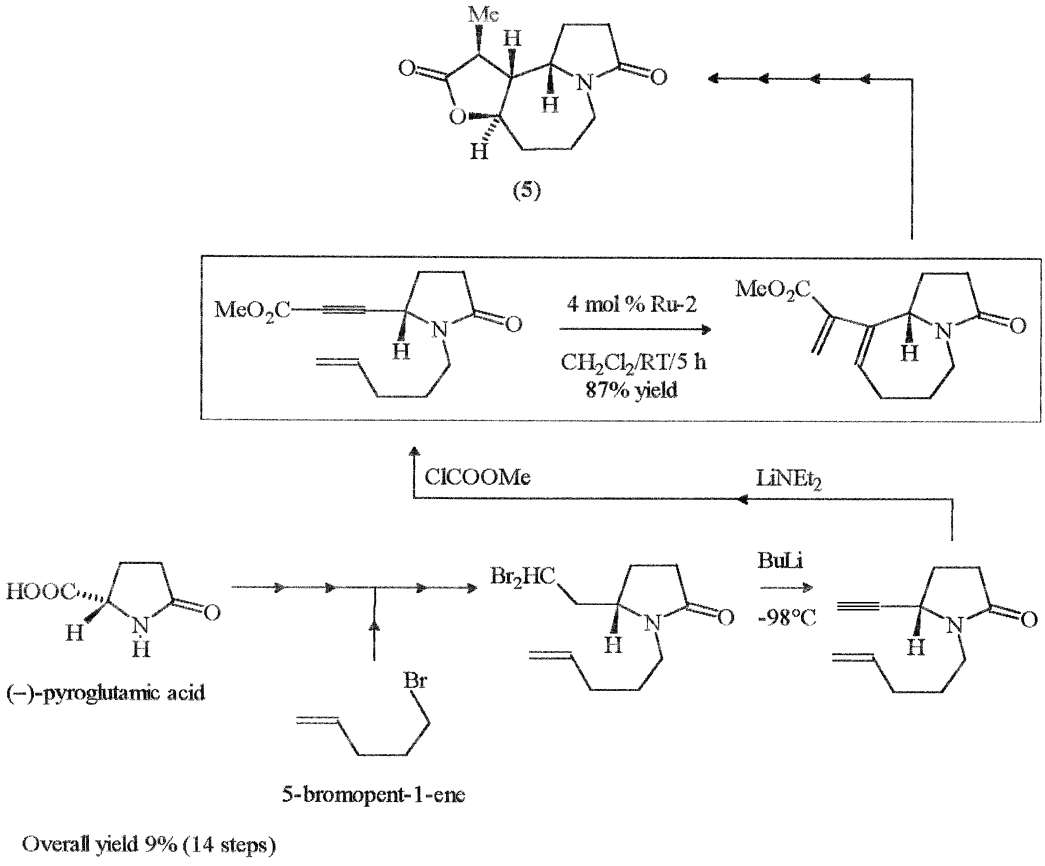


Scheme 3. Synthesis of (±)-dactylol (**4**).

with the sodium salt of the derivative of (−)-pyroglutamic acid in which –COOH has been replaced by $-CH_2OC_2H_4OC_2H_5$. After removing this protecting group, the alkyne group is introduced by means of the following sequence of reactions: $-CH_2OH \rightarrow -CHO \rightarrow -CHBr_2 \rightarrow \equiv CH \rightarrow \rightarrow \equiv CCO_2Me$.

*3.4. Epothilone A (**6**)*

This compound was isolated from the myxobacteria *Sorangium cellulosum* strain 90 and its structure determined by Höfle's group [8] (and references herein). It can be produced on a large scale by fermentation and has very great importance for cancer therapy.



Scheme 4. Synthesis of (−)-stemoamide (**5**).

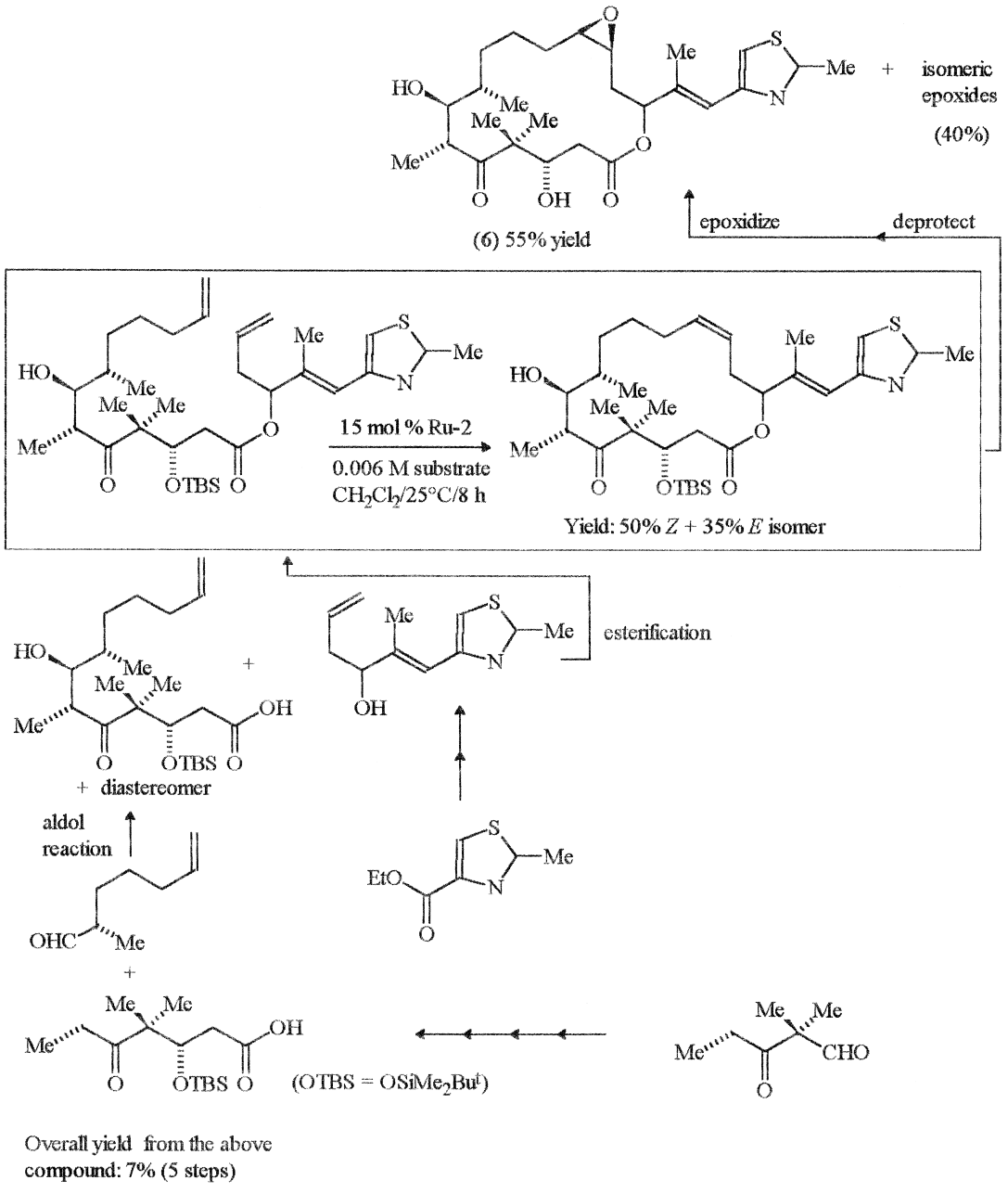
Three groups [9–11] have reported the total synthesis of epothilone by routes using RCM to close the 16-membered ring. Nicolaou's method [9] is shown in Scheme 5.

Unwanted isomers are removed chromatographically at each stage. The substrate for the RCM reaction is produced by an esterification reaction catalyzed by DCC (1,3-dicyclohexylcarbodiimide) in the presence of 4-DMAP (4-dimethylaminopyridine). The RCM reaction, catalyzed by Ru-2, gives the required *cis* isomer in 50% yield. Danishefsky's route [10] gives a better overall yield.

4. Synthesis of sub-units of some natural products

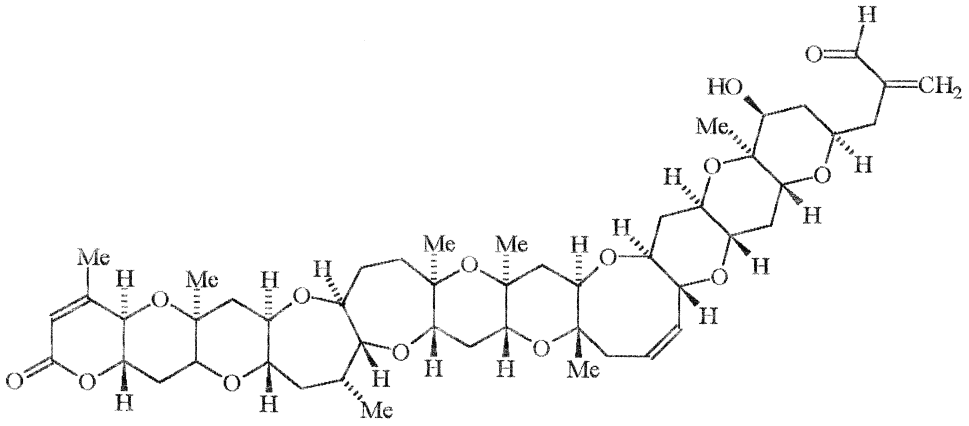
4.1. Brevetoxin B

This is the laddered polyether (**7**) isolated by Nakanishi in 1981 and was the first of a large range of marine toxins to be identified. It contains 11 fused rings containing a sequence of 6, 6, 6, 7, 7, 6, 6,



Scheme 5. Synthesis of epothilone A (**6**).

8, 6, 6 and 6 members. Its total synthesis was reported in 1994, but not using an olefin metathesis reaction; see Ref. [12].



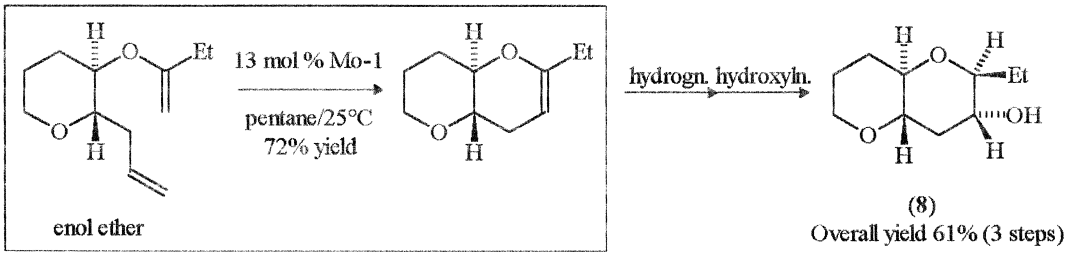
(**7**)

Alternative strategies are now being sought which take advantage of the RCM reaction. An example of the synthesis of a 6,6-bicyclic sub-unit **8** of brevetoxin B is shown in Scheme 6 [13]. Ru-2 is not effective for this RCM reaction. In the subsequent hydrogenation a high level of diastereocontrol is achieved by the use of *t*-hexyl borane as hydrogenating agent.

If the alkenyl substituent in Scheme 6 is lengthened the yield of RCM product falls off. A reasonable yield of a 6,7-bicyclic product can still be obtained, but to make a 6,8 bicyclic compound it is better to use an allyl ether in place of the enol ether (see below).

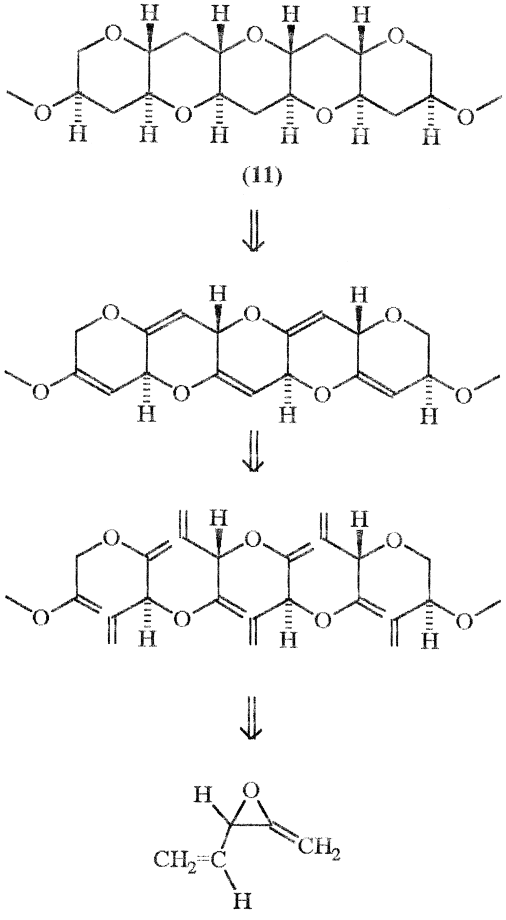
4.2. Brevetoxin A

This is the laddered polyether (**9**) containing 11 fused rings in a sequence of 5, 8, 6, 7, 9, 8, 8, 6, 6 and 6 members.

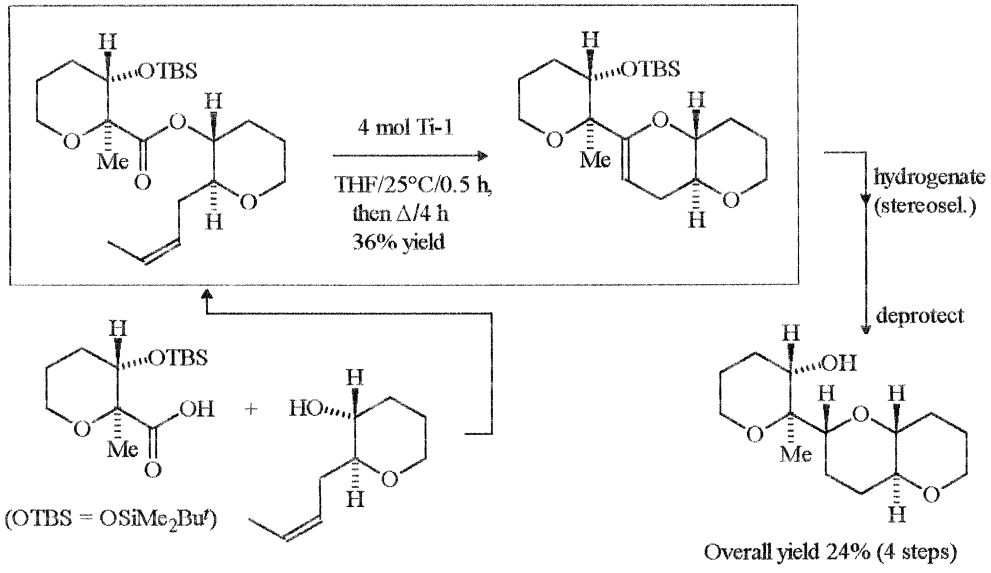


(**8**)
Overall yield 61% (3 steps)

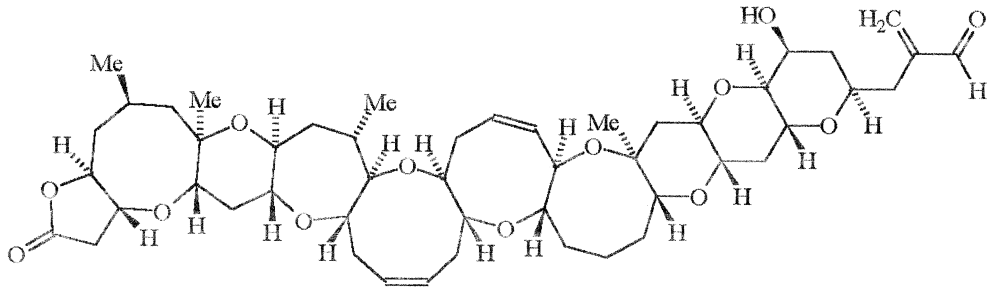
Scheme 6. Synthesis of a sub-unit (**8**) of brevetoxin B.



Scheme 7. Retrosynthesis of an isotactic laddered polyether.

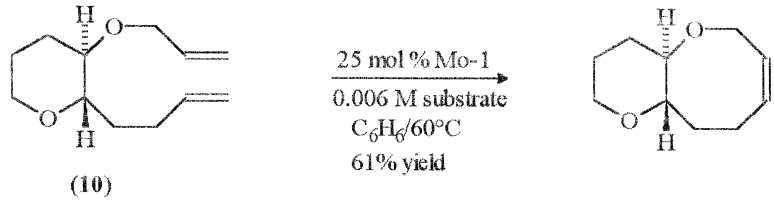


Scheme 8. Synthesis of a sub-unit of maitoxin.



(**9**)

The synthesis of a 6,8-bicyclic sub-unit of **9** can be achieved by the RCM of the allyl ether (**10**) shown in Eq. (4) [14].

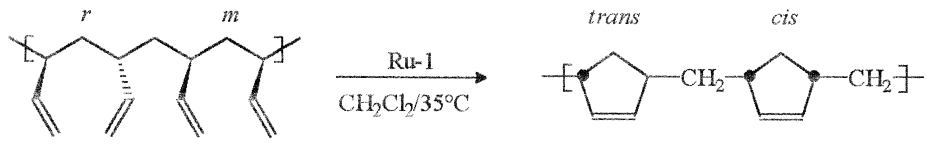


(**10**)

(4)

In passing one may note that the structures of both brevetoxin A and B are based on a polyoxyethene chain with an isotactic sequence of substituents. This prompts the thought that it might be possible to make a model compound (**11**) by following the reverse of the retrosynthesis shown in Scheme 7, using RCM to zip up the ladder.

One may compare this with the somewhat analogous reaction of 1,2-polybutadiene (**12**); reaction (5) [15].



(**12**)

(5)

4.3. Maitoxin

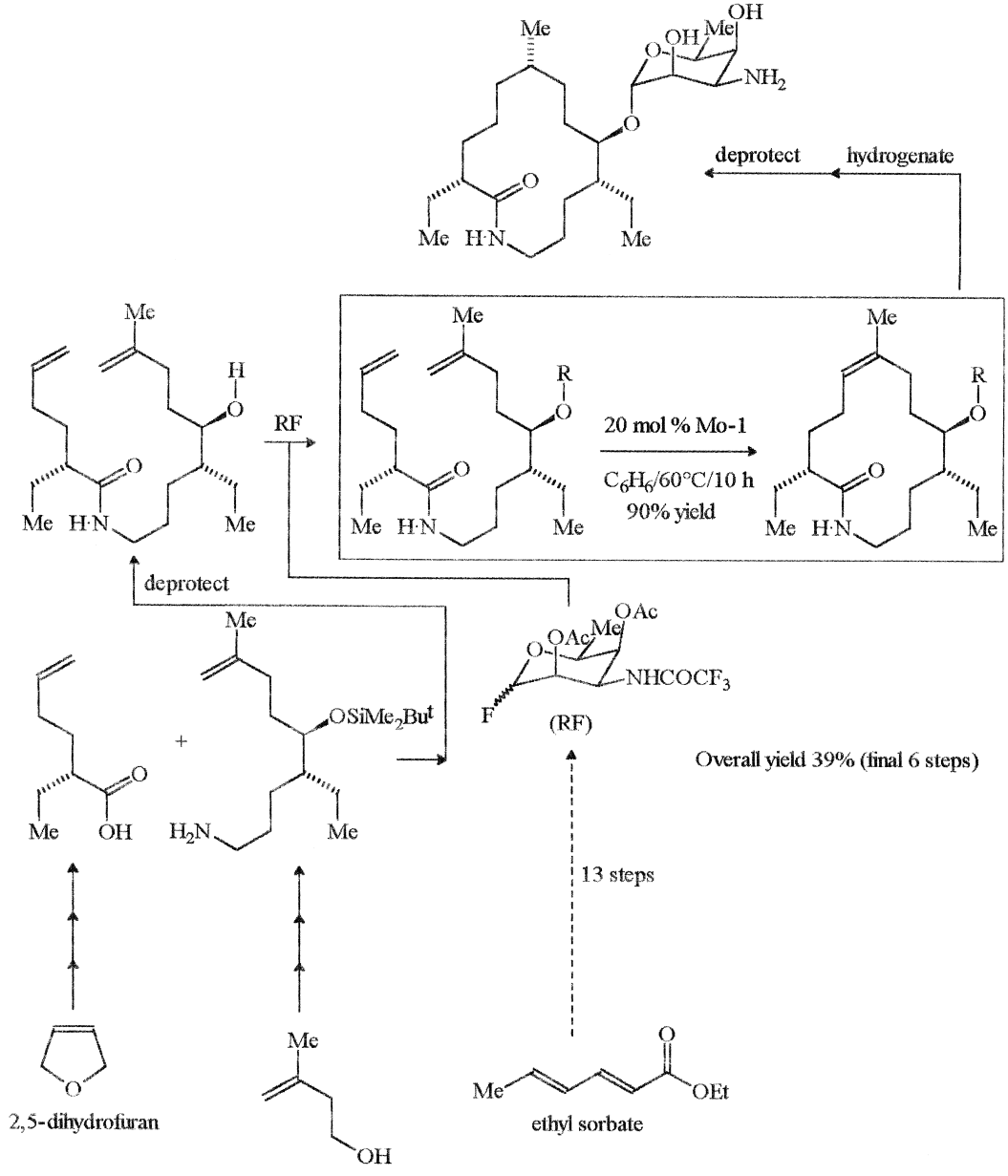
This marine neurotoxin is the most potent non-peptidic substance known to man. It contains 32 cyclic ether units in the form of several laddered structures linked together by single bonds. Means of forming three sub-units of maitoxin, each containing three of these cyclic ether units, have been described [16]. One of these, using the carbonyl–olefination reaction, is shown in Scheme 8.

5. Synthesis of a biologically active agent

5.1. Fluvirucin B_1 (Sch 38516) (**6**)

This compound was discovered at Schering-Plough in 1990 and is an effective agent against the influenza A virus. Its enantiomeric total synthesis by Hoveyda's group is summarized in Scheme 9 [17,18].

The two monoenes are condensed together using the standard peptide condensing agent: DCC with HOBT (1-hydroxybenzotriazole hydrate). The resulting diene is reacted with RF in the presence of $AgClO_4$, $SnCl_2$ and 4 Å molecular sieves to give a single stereoisomer (> 98%) of the lycosylated



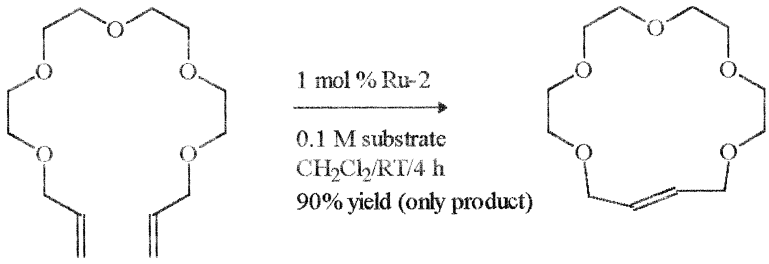
Scheme 9. Enantiomeric total synthesis of fluvirucin B_1.

diene, which is the substrate for the subsequent RCM reaction. The 14-membered ring is formed in good yield by RCM using Mo-1 as catalyst.

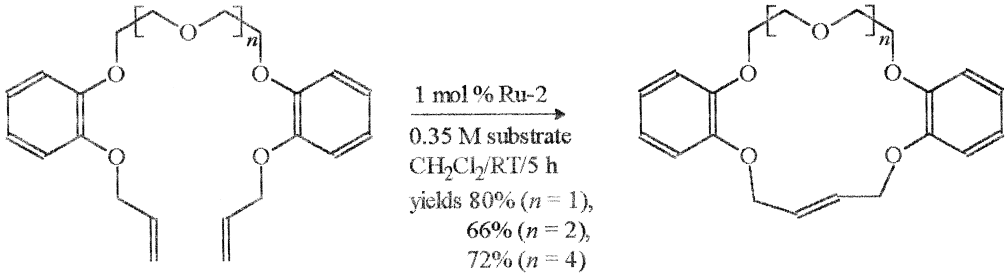
6. Compounds of potential synthetic importance

6.1. Crown ethers

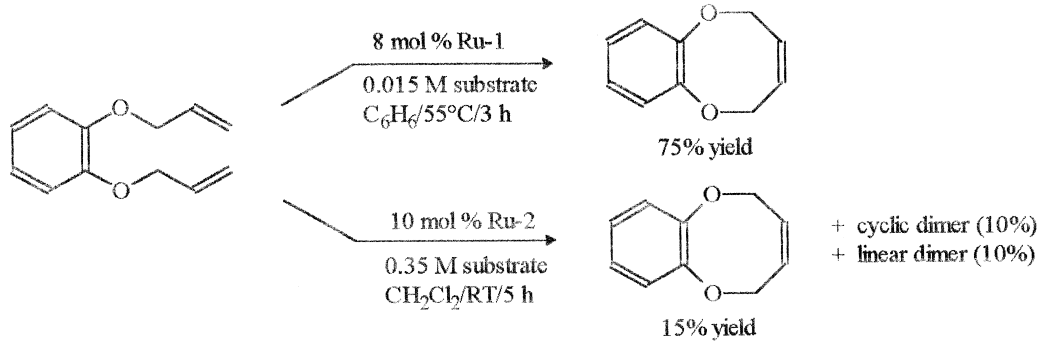
Some examples of the formation of crown ethers by RCM are shown in the following reactions:



(6)



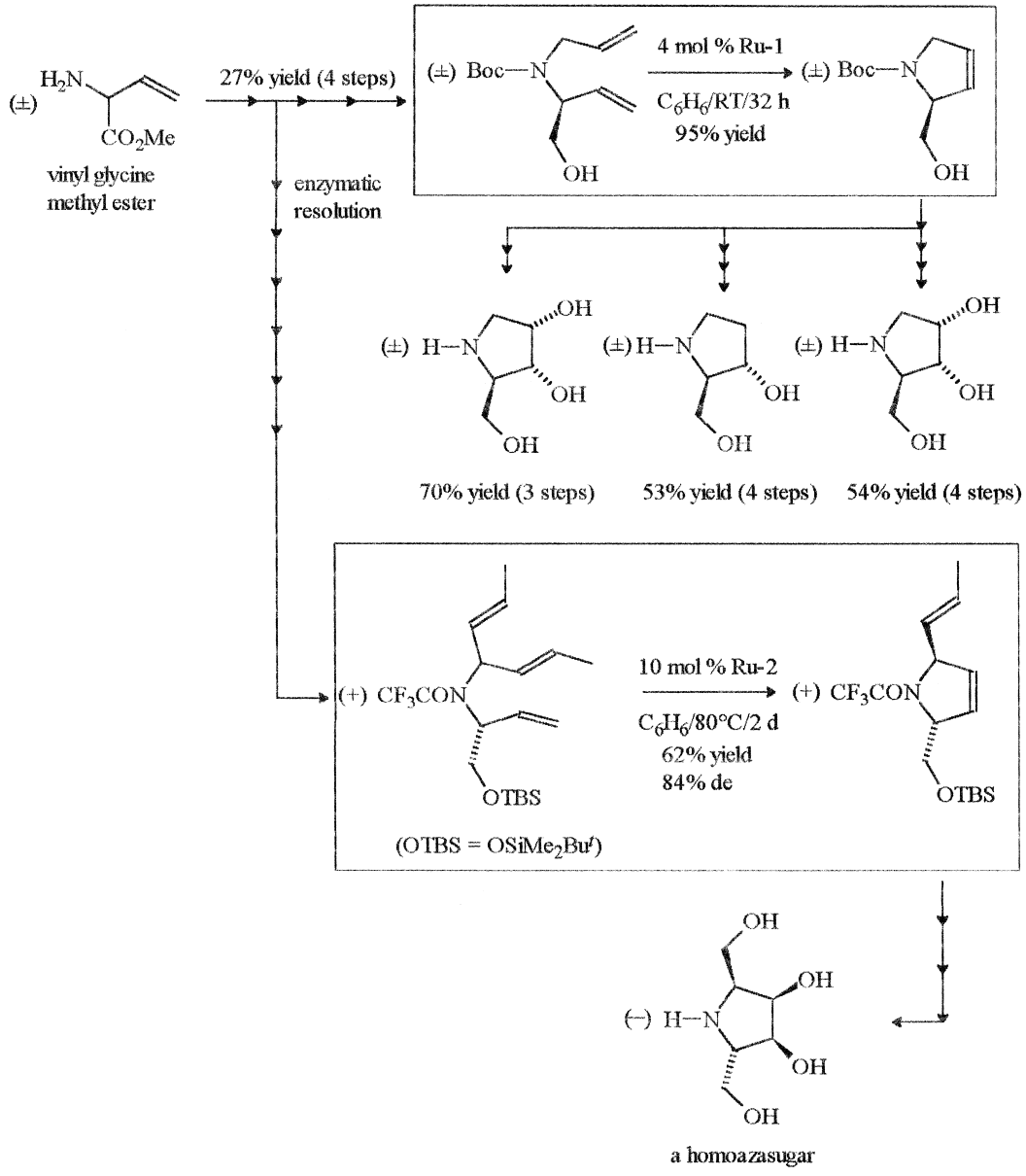
(7)



(8)

(9)

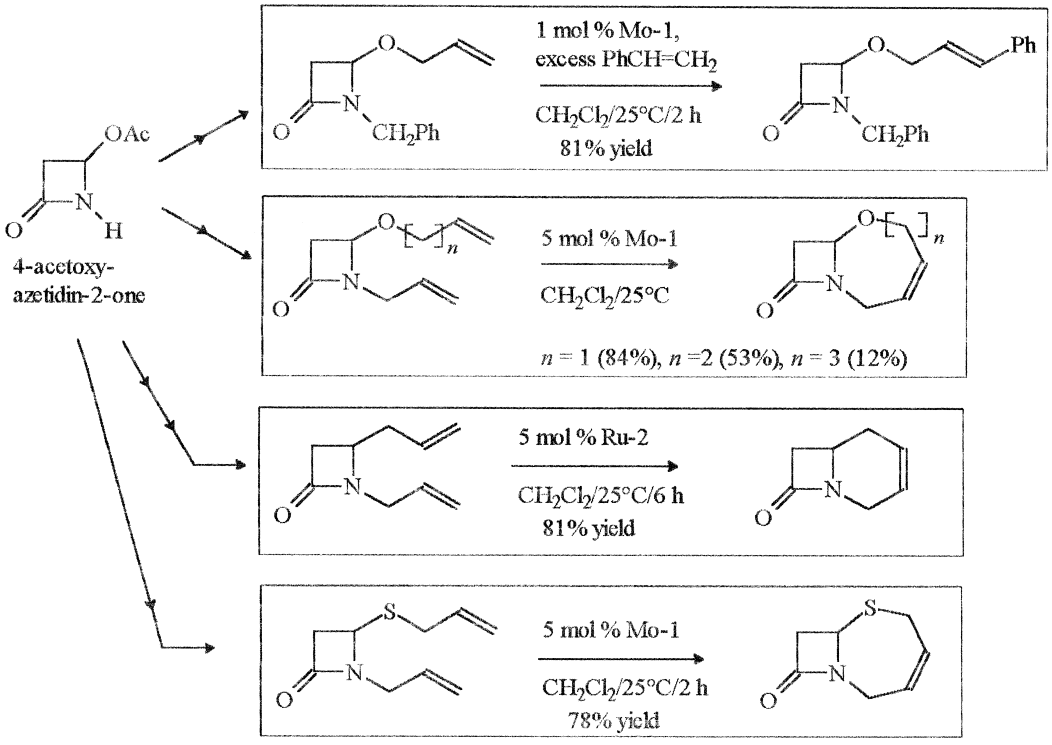
Note that for the second reaction, with $n = 4$, the product is a 26-membered ring formed in good yield (72%) even at moderate substrate concentration (0.35 M) at room temperature [19]. However, for the last reaction a good yield of the RCM product is only obtained if the substrate concentration is much lower (0.015 M) and the temperature somewhat higher (55°C) [20], as expected from thermodynamic considerations [2].



Scheme 10. Synthesis of azasugars.

6.2. Azasugars (polyhydroxylated pyrrolidines)

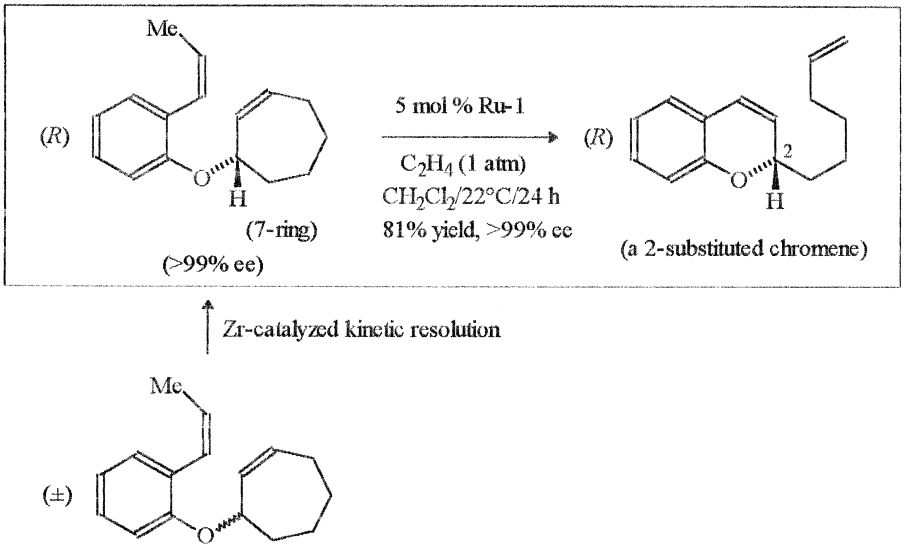
These compounds have potent biological and pharmaceutical activities based on the inhibition of glycosidases, which play an important part in metabolism. Possible applications include therapies of diabetes, cancer and viral diseases. The syntheses of such compounds, starting from vinyl glycine methyl ester and using RCM to form the 5-membered ring, are outlined in Scheme 10 [21].



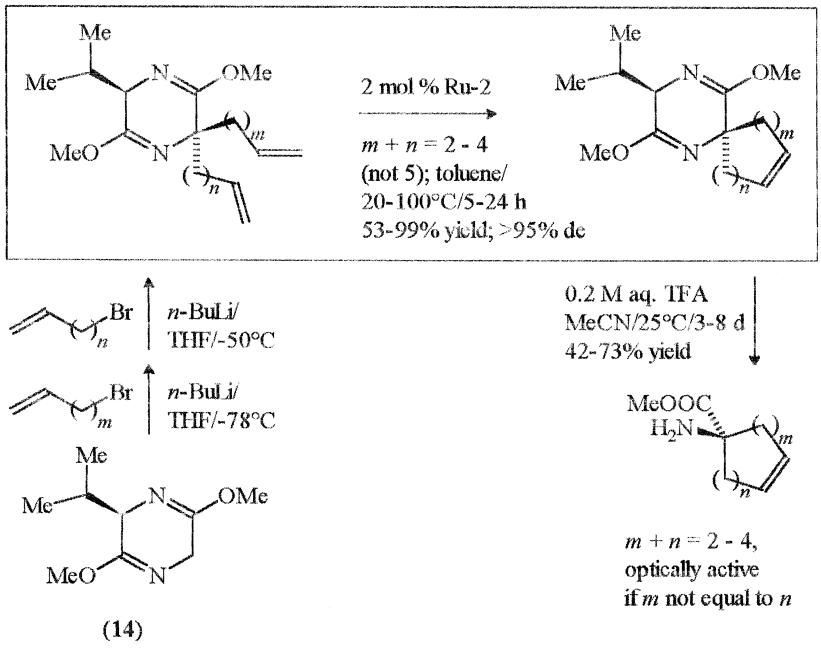
Scheme 11. Synthesis of some novel β-lactams.

6.3. Novel β-lactams

The olefin metathesis reaction has recently been applied to produce a wide variety of new compounds containing the β-lactam structure (cf. penicillin G), as summarized in Scheme 11 [22,23]. Some of these could have important antibiotic properties.



Scheme 12. Synthesis of chromenes.



Scheme 13. Synthesis of α-amino acid esters with the α-carbon incorporated in a ring.

In the first example the allyl ether chain is modified by cross-metathesis with an excess of styrene. In the last example the reaction catalyzed by Ru-2 is much slower and less efficient than that catalyzed by Mo-1.

6.4. Chromenes

The 2-substituted chromene unit is found within a multitude of medicinally important agents. The formation of a 2-substituted chromene by metathesis is illustrated in Scheme 12 [24].

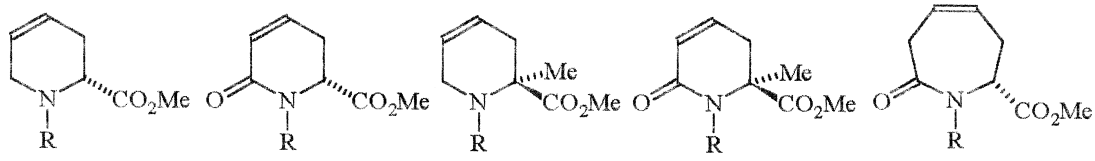
The net result is the opening of the 7-membered ring and the closing of the less strained 6-membered ring. (As expected the reaction does not work for 6- or 5-membered rings in place of the 7-membered ring, but is successful with an 8-membered ring.) There is evidence that [Ru]=CHR reacts first with –CH=CHMe to give –CH=[Ru] which then reacts with the double bond in the 7-membered ring. The function of the ethene is to prevent the occurrence of an intermolecular metathesis reaction leading to 'dimer'. In the preparation of the optically active substrate the Zr-catalyzed resolution is less efficient if the precursor contains the $-CH=CH_2$ group in place of –CH=CHMe.

6.5. Amino acid derivatives

The stereoselective synthesis of α-amino acids where the α-carbon of the amino acid is incorporated into a 5-, 6-, or 7-membered ring has been achieved by the route summarized in Scheme 13 [25].

The stereoselective control results from the stepwise bisalkenylation of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**14**). The second alkenylation proceeds *trans* to the isopropyl group, regardless of the position of the substituent resulting from the first alkenylation. Therefore if $m \neq n$ the ultimate amino acid ester is optically active. When $m = n = 1$ a better yield of final product can be obtained by first hydrolyzing the diene derivative of the pyrazine and then carrying out the RCM reaction.

The preparation of the enantiomeric compounds **15**–**19** by RCM catalyzed by Ru-1 and Ru-2 has been reported [26,27].



(15) **(16)** **(17)** **(18)** **(19)**

7. Conclusion

The olefin metathesis reaction now forms a very important part of the organic chemist's armory and will find increasing use, particularly for stereoselective ring-closing reactions. In the examples given here the metathesis reactions have generally been effected by ready-made metal carbene complexes. However, this should not obscure the fact that many of the older catalyst systems, where the metal carbene initiator is generated in situ, can be equally effective and much cheaper, for example $W(=O)Cl_2(OC_6H_3\text{-}2,6\text{-}Br_2)_2/Et_4Pb$ $(1/2)$ for the RCM of acyclic dienes to afford 5-membered cyclic compounds that are intermediates in the synthesis of carbocyclic nucleoside analogues [28].

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