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SYNTHESIS OF MACROCYCLIC COMPOUNDS BY RING ENLARGEMENT

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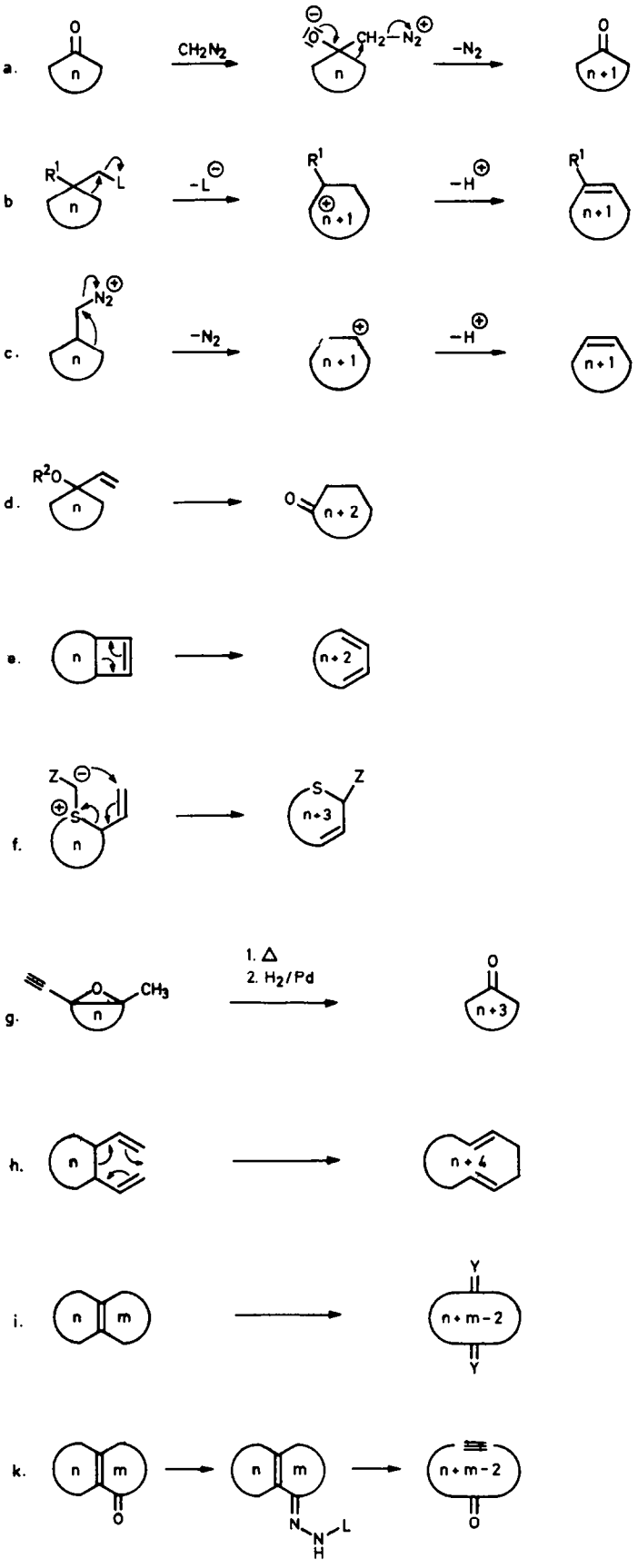
CONTENTS

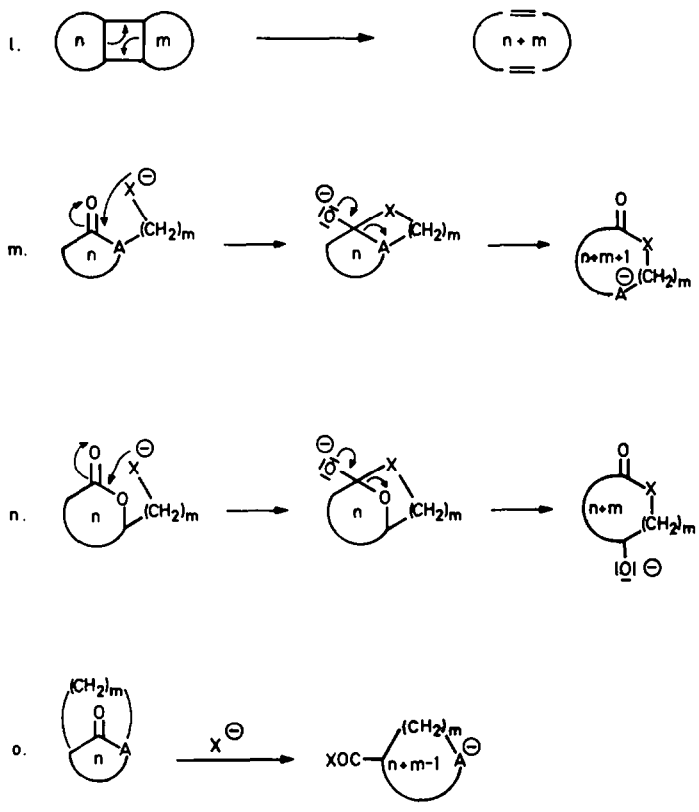
Abstract—A summary of important ring expansion strategies, including recent references, is presented in Section 1. Subsequently the synthesis of macrocyclic ketones, lactams and lactones involving the heterolytic cleavage of the bridge bond in bicyclic intermediates is discussed. Typical applications in the field of natural product synthesis are shown. Finally the ring enlargement strategies are compared, pointing out the advantages and drawbacks of each method.

1. INTRODUCTION

A comprehensive review of ring expansion reactions was published by Gutsche and Redmore in 1968.[1] Since then research in this field has increased enormously. Recent review articles are therefore restricted to more specialized subjects.[2] Our efforts were concentrated on the synthesis of macrocycles by means of ring enlargement reactions via heterolytic cleavage of the bridge bond in bicycles. This will be the principal subject of this Report. First of all a short summary of general ring enlargement strategies and some selected references are presented. In Scheme 1 the reactions are listed according to the number of atoms being incorporated in the ring enlarging step. Representing formal 1,2-migrations, the transformations **a**, **b** and **c** lead to carbocyclic compounds augmented by one atom. Example **a** illustrates the Wolff rearrangement[3,4] which can be related to the Schmidt,[5] Baeyer–Villiger[6] and the Tiffenau[7] reactions. Pinacol[8] and α-ketol[9] type rearrangements proceed by a similar mechanism. The Wagner–Meerwein[10] (example **b**) and the Demjanov[11] (example **c**) reactions have also been used for ring enlargement reactions. Other methods for the insertion of one atom to a cyclic system are the dienone-phenol[12] and the Beckmann[13] rearrangements as well as the fragmentation reactions of carbene adducts.[14] Example **d** can be interpreted as a formal 1,3-migration of allylic alcohols or ethers[15] leading to (n+2)-membered rings. Thermal cycloreversion of [2+2]-cyclo adducts[16] (example **e**) also results in carbocycles expanded by two atoms. In the transformations **f** and **g** the original ring is enlarged by three atoms. Transformation **f** shows a [3,2]-sigmatropic rearrangement of S-alkylated 2-vinylthiacycloalkanes.[17] Transformation **g** illustrates the thermolysis of 1-alkynyl-2-methyl-1,2-epoxycycloalkanes.[4,18] Expansion of cyclic compounds by four atoms can



Scheme 1.

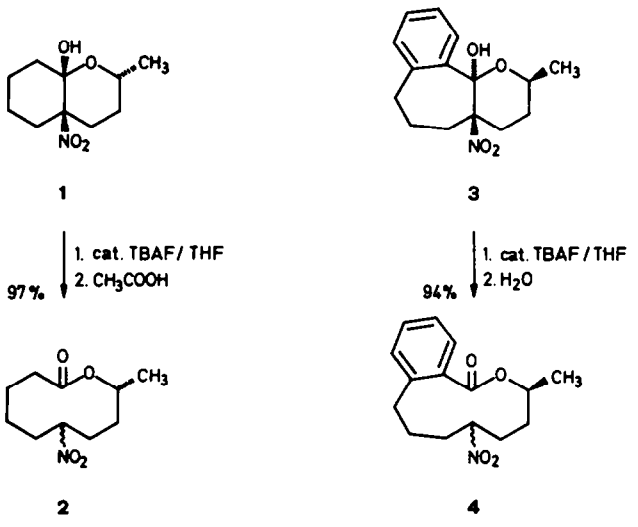


Scheme 1. *continued*

be achieved by the Cope rearrangement[19] as shown in example **h**. Beside the reactions mentioned so far, in which a specific number of atoms is being incorporated to an existing ring, there are other methods of ring enlargement, allowing expansions by a variable number of atoms. Examples pointing out these strategies are the oxidative cleavage of bridge bonds in bicyclic systems[20] (example **i**), the α,β-enone-alkynone fragmentation[21] (example **k**) and the thermal cycloreversion of tricyclic [2+2]-adducts[16] (example **l**). The reactions shown in **m**, **n** and **o**, do in principle permit the incorporation of any number of atoms into a starting ring. Our work concentrated on these latter reactions and their application in the synthesis of macrocyclic ketones, lactams and lactones[22] so this matter will be discussed in more detail in the following Sections.

2. HETEROLYTIC CLEAVAGE OF THE BRIDGE BOND IN BICYCLIC SYSTEMS

In examples **m** and **n** (Scheme 1) the residue X represents an internal nucleophile which attacks the carbonyl carbon atom, giving a bicyclic intermediate. Either oxygen, nitrogen, or carbon nucleophiles have been used. The residue A (example **m** and **o**) represents an electron acceptor. This can be an atom like nitrogen or a carbon atom carrying an electron withdrawing group such as COR, SO_2R, NO_2, CN and $CH_2NR_3^+$. NO[23] and COOR[24] groups can, in principle, also be used. The ring enlarging step consists of a heterolytic cleavage of the bridge bond in the bicyclic intermediate. In example **o**, the cleavage of the σ-bond from the carbonyl carbon atom towards the electron acceptor A is achieved by the attack of an external nucleophile X. In some cases[25-27] the bicyclic intermediates outlined in Scheme 1 (example **m**) could be isolated and by further treatment with base, they yielded the expected ring enlargement products. The relative configuration of the substituents of the bicycles **1** and **3** (Scheme 2) was determined by X-ray structure analysis. Both intermediates although having different stereochemistry undergo ring expansion to **2** and **4** respectively under basic conditions. Either the stereochemical arrangement of the OH and the NO_2 groups does not affect the course of the reaction or one of the diastereoisomers is not the direct precursor of the corresponding ring expanded product. In the latter case, base-catalyzed

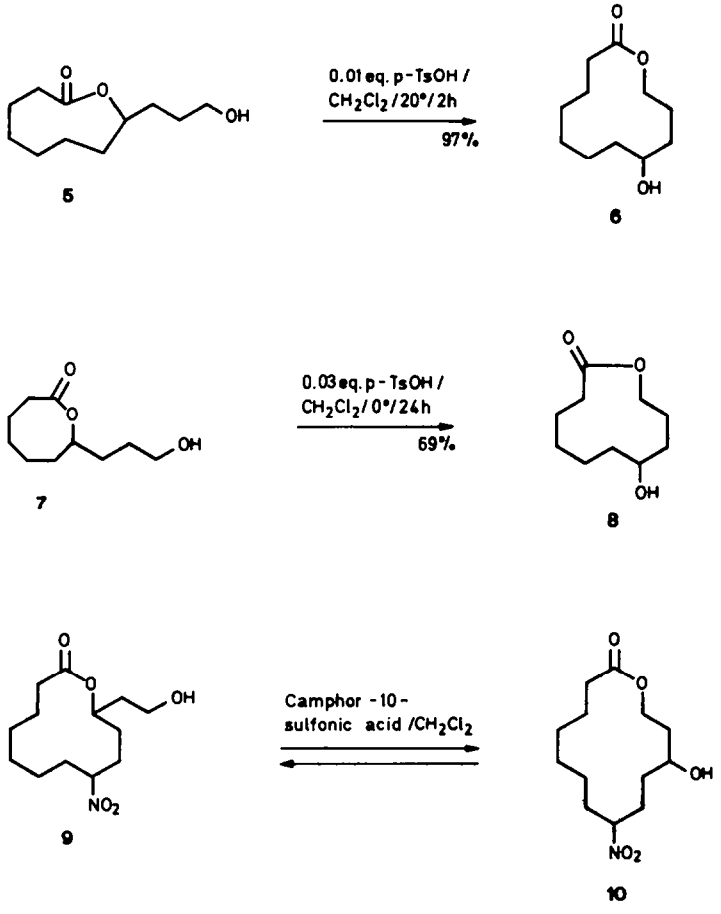


Scheme 2.

epimerisation of the hemiacetal function in **1** or **3** could first generate the appropriate diastereoisomer which is then capable of undergoing ring expansion.

3. TRANSLACTONIZATION REACTIONS

Intramolecular transesterification reactions (translactonizations)[28] are catalyzed by base as well as by acid: they proceed under thermodynamic control (Scheme 3). The driving force for these



Scheme 3.

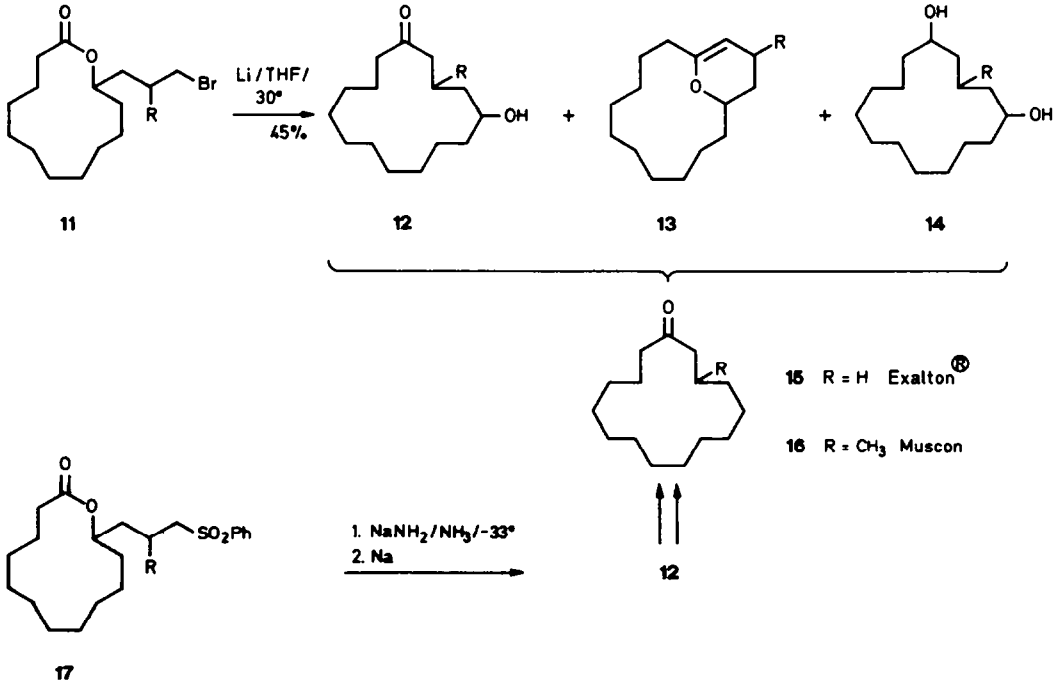
transformations is the release of ring strain of a thermodynamically unstable medium sized ring. Thus the 9-membered lactone **5** reacts rapidly, giving the 12-membered lactone **6** in high yields, whereas the formation of the 12-membered lactone **8** starting from **7** is less favoured: the yield is lower and there are considerable amounts of side products, especially polymerized compounds. A similar translactonization of a 7-membered ε-caprolactone derivative is not possible due to the stability of the 7-membered ring system. Another factor influencing these rearrangements is the length of the side chain to be incorporated into the original ring. By increasing the length, the reaction rate is reduced so that the incorporation of four carbon atoms through an 8-membered intermediate did not succeed.[28] On the other hand, the treatment of the 12-membered 13-hydroxy-8-nitro-11-tridecanolide (**9**) with camphor sulfonic acid produced a mixture of starting material and the 14-membered lactone **10**.[29] In this expansion by two carbon atoms a 6-membered intermediate is involved. The release of ring strain during this reaction should be quite insignificant so both compounds (**9** and **10**) remain in a thermodynamic equilibrium of approximately 1 : 1.

4. TRANSFORMATIONS OF LACTONES INTO MACROCARBOCYCLES

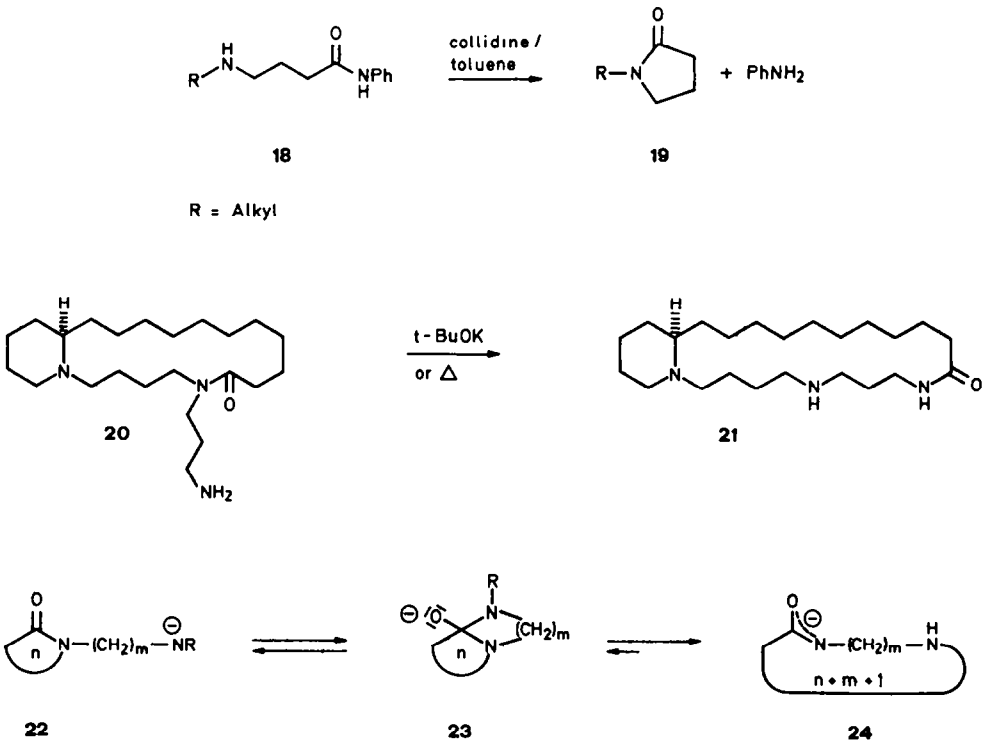
An elegant ring expansion strategy has been developed for the synthesis of Exalton® (**15**) and muscone (**16**).[30] The intramolecular attack of a carbanion on the lactone carbonyl carbon atom of **11** and **17** respectively (Scheme 4)[31] gives rise to ring enlarged carbocycles with the incorporation of three carbon atoms. Generation of the carbanion may be accomplished by adding a metal (preferably Li in THF) to the bromide **11**, leading to a mixture of **12**, **13** and **14** in approximately 45% total yield. In a subsequent reaction step the mixture was transformed into **15** or **16** respectively. The phenyl–sulfonyl lactones **17** upon treatment with $NaNH_2/NH_3$ in THF followed by reductive removal of the phenyl–sulfonyl residue with elemental sodium were converted into **12** in yields of 81 (R = H) and 60% (R = CH_3), respectively. This multistep transformation can be realized as a one pot procedure.[31]

5. TRANSAMIDATION REACTIONS

The intramolecular aminolysis of amides of the general formula **18** (Scheme 5) has been extensively investigated in 1958.[32] Later on, the fact that neooncinotine (**20**) could be completely trans-

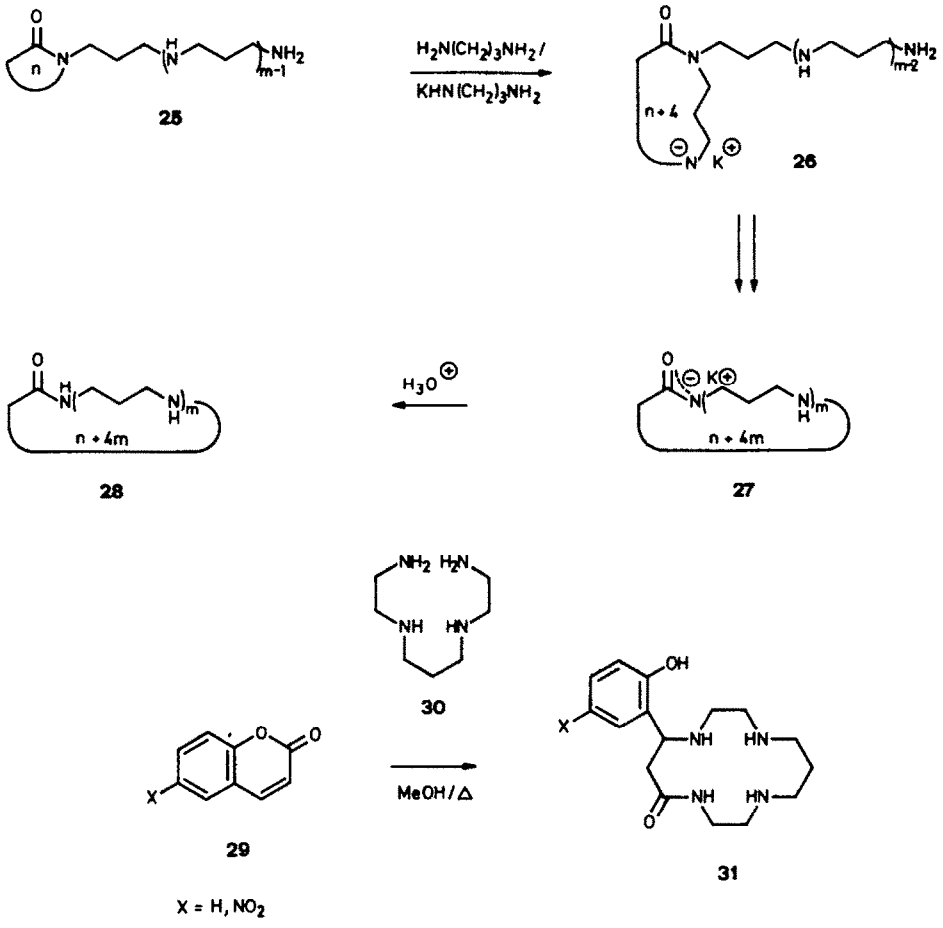


Scheme 4.



Scheme 5.

formed into isooncinotine (**21**), either thermally or base catalyzed (Scheme 5),[33] led to a series of systematic investigations in order to examine the generality of such isomerizations. Beside steric effects, the conversion of the initially generated anion **22** into the comparatively stable amide anion **24** can be regarded as the driving force of these reactions (see also[34]). Thus starting from 8-, 9- and 11-membered lactams the corresponding 12-, 13- and 15-membered transamidation products are obtained in high yields. These reactions are conveniently carried out with *t*-BuOK/toluene or with potassium-3-aminopropyl amide (KAPA)/1,3-diaminopropane. However, under these conditions the 7-membered N-(3-aminopropyl)-ε-caprolactam gave only the corresponding amidine 1,8-diazabicyclo[5.4.0]undec-7-en (DBU).[35] This amidine could not be transformed into a ring enlarged azalactam but similar conversions were successfully carried out with higher homologues.[36] Since the expanded products are again lactams, ring enlargement can be repeated stepwise. Starting from the N-substituted lactams of type **25** (Scheme 6), successive incorporation of aminopropyl units produces the (n+4m)-membered polyaza-lactams **28** in a way resembling the working mode of a zip. By this so-called zip-reaction, macrocycles with up to 53 ring atoms were synthesized.[37] The coumarin derivatives **29** can be converted into **31** in a similar way.[38] Probably the first step in this transformation is the conjugate addition of a primary amino group of **30** to the α,β-unsaturated lactone **29**, followed by lactone aminolysis and two transamidation reactions. Further examples involving incorporation of aminoethyl and aminobutyl units through 5- and 7-membered intermediates respectively (compound **23**, m = 2 or 4) have also been reported.[39] Again increasing the length of the side chain (see Section 3) results in lower reaction rates. By these methods, medium sized rings can be converted into large rings with the insertion of preferably three or four atoms in each transamidation step. Due to the stability of the anion **24**, translactamizations run to completion even if there is no obvious release of ring strain during the process (in contrast to translactonizations, see Section 3). However, the formation of strained medium sized rings starting from normal rings is not favoured. Suitable substituted normal rings may be completely transformed into large rings via unstable medium sized intermediates.[40] Thus treatment of the barbituric acid derivative **32** (Scheme 7) with KF gave the 14-membered compound **34** through the 10-membered intermediate **33**. Transamidation of highly strained small rings can, however, lead to medium sized lactams.[33] Another example related to this reaction type is the ring expansion of N-(3-aminopropyl)glutarimide.[41]

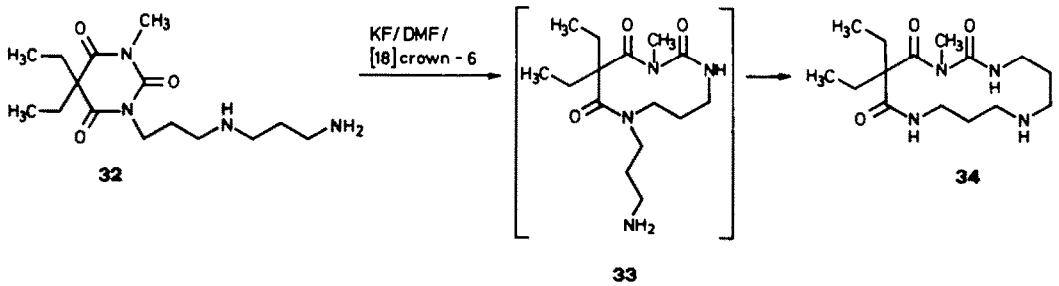


Scheme 6.

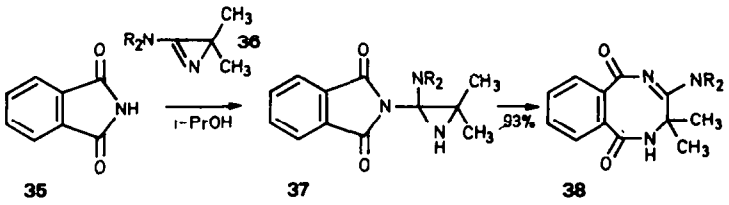
The transamidation reactions have been successfully applied in the synthesis of polyamino-alkaloids. Recently the natural products celacinnine,[42] homaline,[43] chaenorhine,[44] verbascenine,[45] and desoxoinandenine[46] were synthesized using the zip-reaction. In a similar way 3-amino-2H-azirine derivatives react with various cyclic compounds giving ring enlarged heterocycles.[47] A typical example for this reaction principle is shown in Scheme 8. In the first step phthalimide (**35**) protonates the aminoazirine **36** thus enhancing its electrophilicity. This is followed by generation of the intermediate **37** which rearranges to the ring expanded benzodiazocine derivative **38**. Beside phthalimide (**35**), malonimide and saccharin also undergo this type of reaction.

6. RING ENLARGEMENT OF OXOCARBOCYCLES

As mentioned in the introduction, the concept of ring enlargement via heterolytic cleavage of bridge bonds may also be extended to oxocarbocycles if the carbon atom adjacent to the carbonyl



Scheme 7.



Scheme 8.

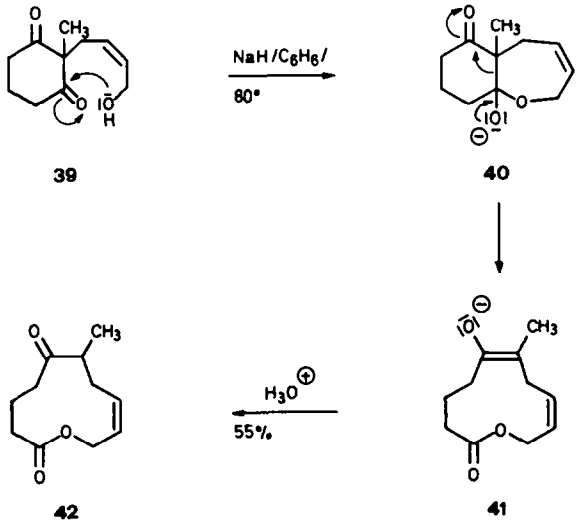
group bears an electron withdrawing group. The reactions can be classified according to the nature of these auxiliary groups.

6.1. *Cycloalkan-1,3-diones*

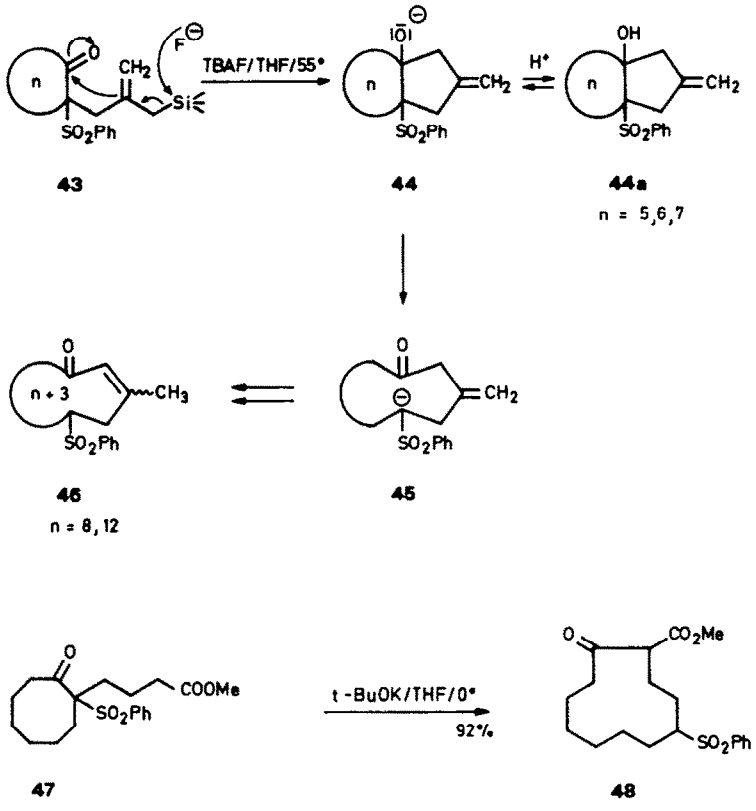
This section summarizes reactions in which the electron withdrawing moiety is an additional carbonyl group. As shown in Scheme 9 the 11-membered lactone **42** has been obtained in moderate yields starting from the 1,3-dione **39**.[48] The course of the reaction corresponds to that of a retro-Claisen ester condensation. One disadvantage of this method is the difficult access to medium sized cycloalkan-1,3-diones which would be required for the synthesis of larger lactones. In a systematic investigation the length of the hydroxyalkyl side chain in compounds similar to **39** has been varied. Best yields of ring expanded products are obtained if 5- or 6-membered rings are generated in the intermediate (similar to **40**). By increasing the length of the side chain, yields drop drastically and reach a minimum if a 9-membered intermediate is involved. With nine methylene groups in the side chain, leading to a relatively favoured 12-membered intermediate, yields rise up to 56%, and the drop to 11% if 20 methylene groups are to be incorporated.[49] For further reports dealing with the synthesis of 9- to 11-membered ketolactones via retro-Claisen type reactions, see.[50]

6.2. 2-*Phenylsulfonyl cycloalkanones*

A phenylsulphonyl residue in the α-position to a carbonyl group also enhances the lability of the α-bond. Scheme 10 presents ring enlargement reactions using carbanions as internal nucleophiles. In the first example, (n+3)-membered macrocarbocycles are prepared.[51] The compounds **43** (n = 8 and 12) upon treatment with 0.2 eq. tetrabutylammonium fluoride (TBAF) in THF at 55° gave the corresponding 11- and 15-membered carbocycles **46** in yields of 90 and 92% respectively. Compound **46** (n = 12) was transformed to muscone (**16**, Scheme 4) by catalytic hydrogenation and reductive removal of the phenylsulphonyl group. For n = 5, 6 and 7, only the bicycle **44a** was obtained. Under drastic conditions (KH/[18]crown-6/DME) compound **44a** (n = 5) undergoes ring expansion with simultaneous $PhSO_2$ elimination, producing 3-methyl-2,4-cyclooctadienone in 80% yield. Similar



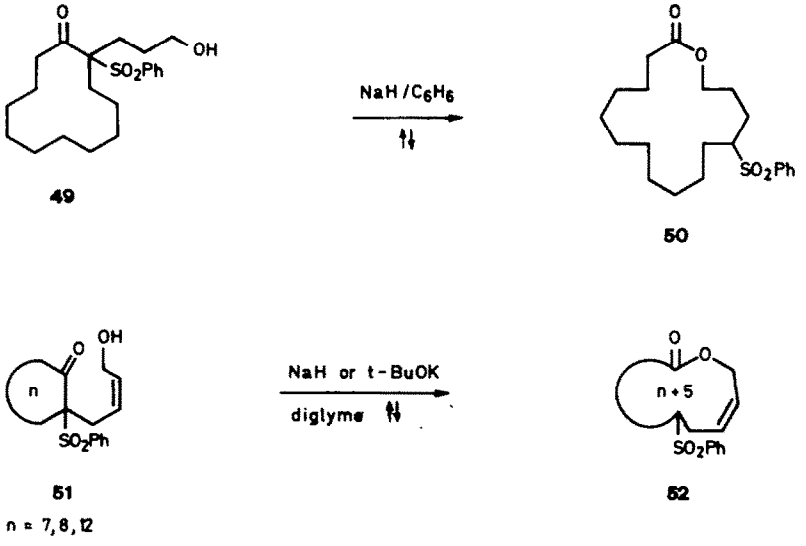
Scheme 9.



Scheme 10.

treatment of the 6- and 7- membered analogues also led to $PhSO_2$ elimination products. Again it can be seen that the reaction path is facilitated by release of ring strain during the ring expansion step. An activated methylene group can also be used as an internal nucleophile. With strong base (3.5 eq. *t*-BuOK/THF) compound **47** can be converted to its corresponding ester enolate anion which then reacts giving the carbocycle **48** in 92% yield.[52]

Alkoxides can also serve as internal nucleophiles for ring expansion reactions (Scheme 11).[53] Under basic conditions the hydroxyalkyl derivatives **49** and **51** lead to the lactones **50** and **52** with



Scheme 11.

insertion of four or five additional ring atoms respectively. These reactions were carried out with NaH in refluxing benzene or diglyme, giving the desired products in satisfactory yields. Compound **51** (n = 6) had to be treated with *t*-BuOK in refluxing diglyme in order to afford the corresponding 11-membered lactone. Compound **51** (n = 5) did not undergo ring expansion even under these conditions. The (Z)-double bond in the compounds of general formula **51** is essential for these lactonization reactions. Corresponding dihydro derivatives did not undergo ring enlargement. Compounds **50** and **52** can be transformed into unsubstituted macrocyclic lactones by conventional methods. Some of them are flavoring compounds frequently used in perfumes and fragrances.

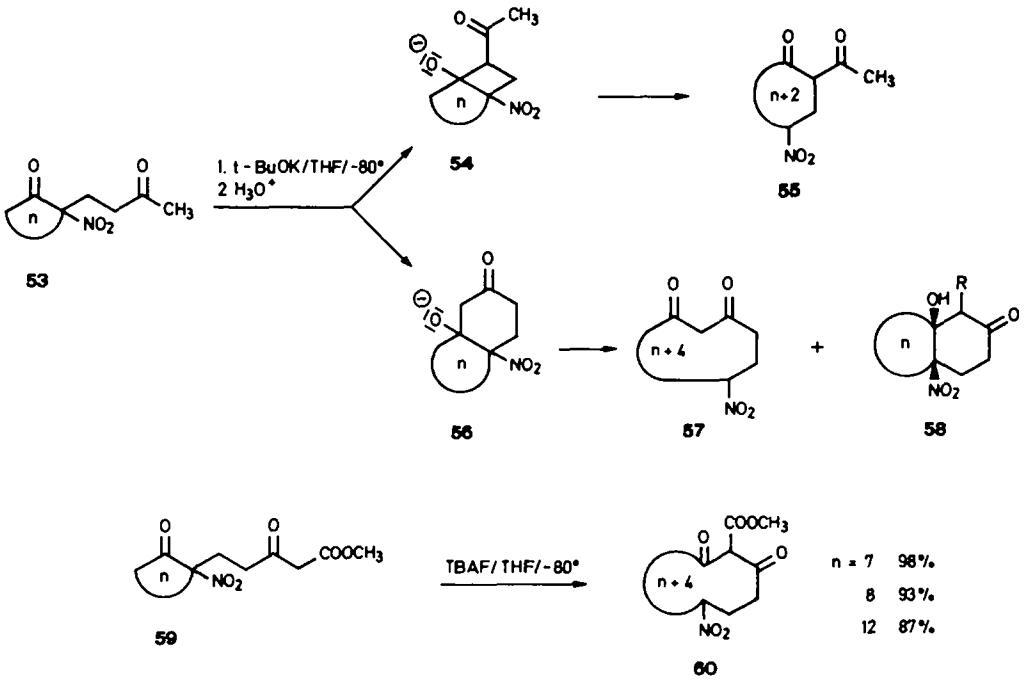
6.3. 2-*Nitrocycloalkanones*

The heterolytic cleavage of the C(1)–C(2) bond of 2-nitroketones has been extensively investigated. The synthesis of 2-nitroketones and their reactions with external nucleophiles has been comprehensively reviewed.[54] Suitable 2-substituted 2-nitrocycloalkanones can also be cleaved by the reaction with an external nucleophile. The resulting open chain compounds represent useful organic building blocks.[55] On the other hand, reaction with internal nucleophiles can afford ring enlarged products. Thus, compounds with the general formula **53** (Scheme 12) when treated with 2 eq. *t*-BuOK in THF at −80° gave a mixture of **55** (incorporation of two carbon atoms) and **57** (four carbon atoms). Compound **53** (n = 6) gave exclusively the 8-membered diketone **55** whereas the homologue (n = 7) produced a mixture of **55**, **57** and the bicycle **58**.[25]

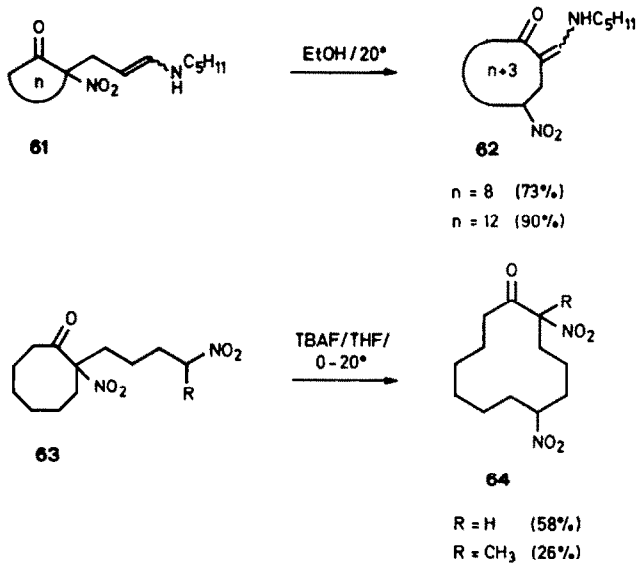
By enhancing the acidity of the active methylene group situated in the side chain (see **59**, Scheme 12), the ring expansion takes place regiospecifically by insertion of four carbon atoms. With n = 7, 8 and 12, formation of **60** proceeds in excellent yields using 2.1 eq. TBAF in THF at −80°. However, the same reaction with **59** (n = 5 or 6) does not afford the desired 9- and 10-membered carbocycles respectively. Even under more drastic conditions, only bicyclic compounds (**58**, R = $COOCH_3$) were isolated.[25] For a detailed discussion concerning the mechanism of this type of reaction and for similar reactions starting from α-nitrobenzocycloalkanones see.[56]

In situ generated enamines of the general formula **61**[57] as well as 2-(4-nitroalkyl)-2-nitrocyclooctanone (**63**)[58] also undergo ring expansion reactions as shown in Scheme 13. In principle the latter reaction represents a repeatable ring enlargement since the product **64** is again a 2-nitroketone.

In contrast to translactonizations and transamidations which are definitely reversible processes, the reversibility of the reactions discussed above has not yet been established. Application of the

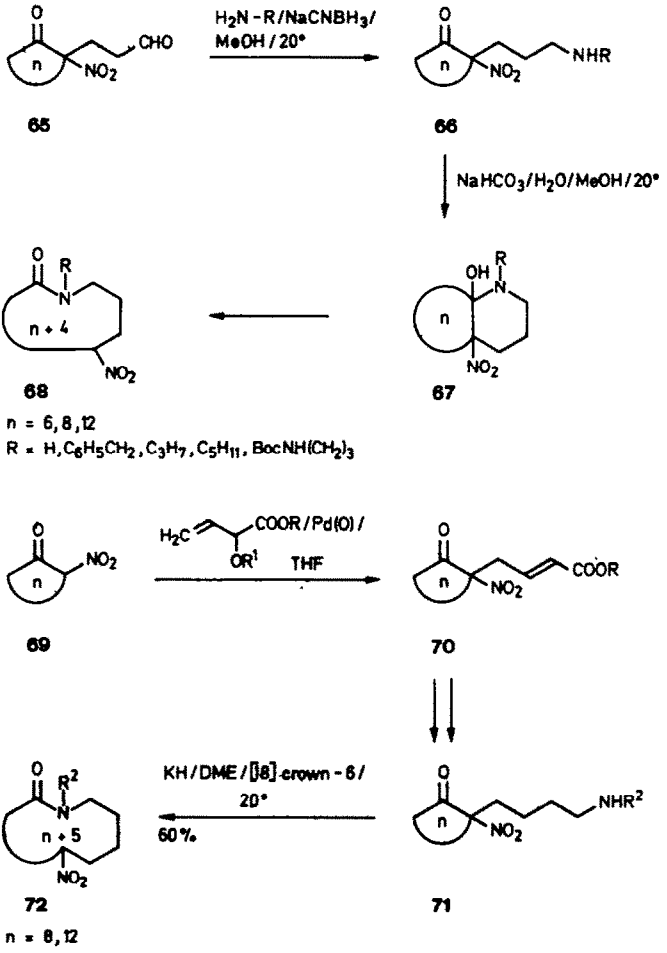


Scheme 12.

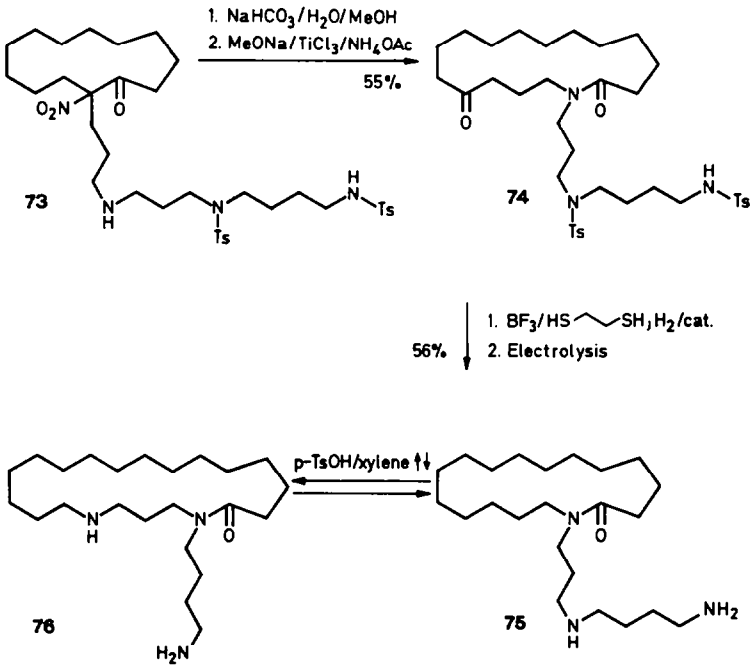


Scheme 13.

same reaction principle for the synthesis of macrocyclic lactams have also been reported.[59] Reductive amination of the aldehydes of general formula **65** (Scheme 14) with ammonia or primary amines and $NaCNBH_3$ affords the amines **66**. For R = alkyl or benzyl they can be isolated as hydrochlorides. With R = H and n = 6 or 12, the reductive amination gave directly the lactams **68** in about



Scheme 14.



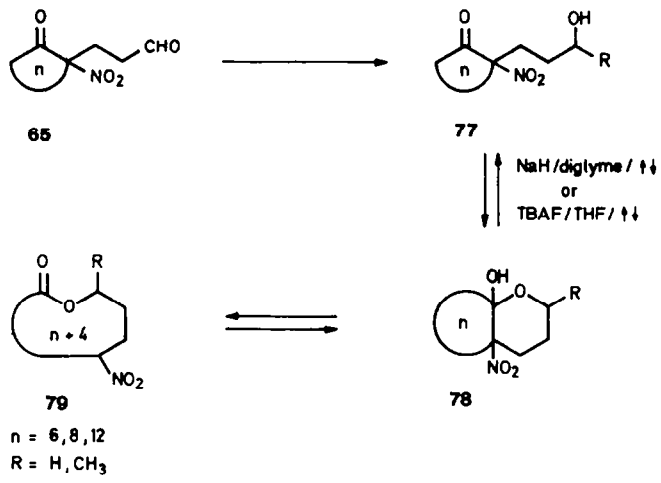
Scheme 15.

40% yield. With n = 8, only traces of a ring enlargement product were detected. Rearrangement of the secondary amines **66** (R = benzyl, C_3H_7, C_5H_{11} or $BocNH(CH_2)_3$) by treating their corresponding hydrochlorides with saturated $NaHCO_3$ solution yielded **68** in 50 to 95%. Only with **66** (n = 8, R = C_3H_7) the reaction did not take place.[59] The same reaction principle was applied in the synthesis of macrocyclic benzolactams starting from 1-tetralone and benzosuberone derivatives.[60] In a similar way the spermidine alkaloid, desoxoinandenine (**76**, Scheme 15), was synthesized.[46] Compound **73** (obtained by reductive amination of **65**, n = 13) was first rearranged to a 17-membered nitrolactam which after $TiCl_3$ promoted Nef reaction[61] gave the ketolactam **74**. Reductive removal of the keto function as well as electrolytic removal of the tosyl protecting groups afforded the lactam **75**. Under acidic conditions, **75** and the desired **76** are in thermodynamic equilibrium (~1 : 1).

In contrast to other C–H acidic compounds, 2-nitroketones generally do not undergo nucleophilic substitution with alkyl halides. Therefore the investigations mentioned so far, always started from Michael addition products. However, by means of Pd(O) catalyzed alkylation of 2-nitrocycloalkanones,[62] it is possible to introduce other substituents in position 2 (Scheme 14, **69** → **70**). Using this approach, the amines of general formula **71** (Scheme 14) could be synthesized. They can be rearranged to **72**, thus introducing five atoms to the former ring system. Drastic conditions (KH/diglyme) are necessary for these transformations and the yields are only moderate.[63]

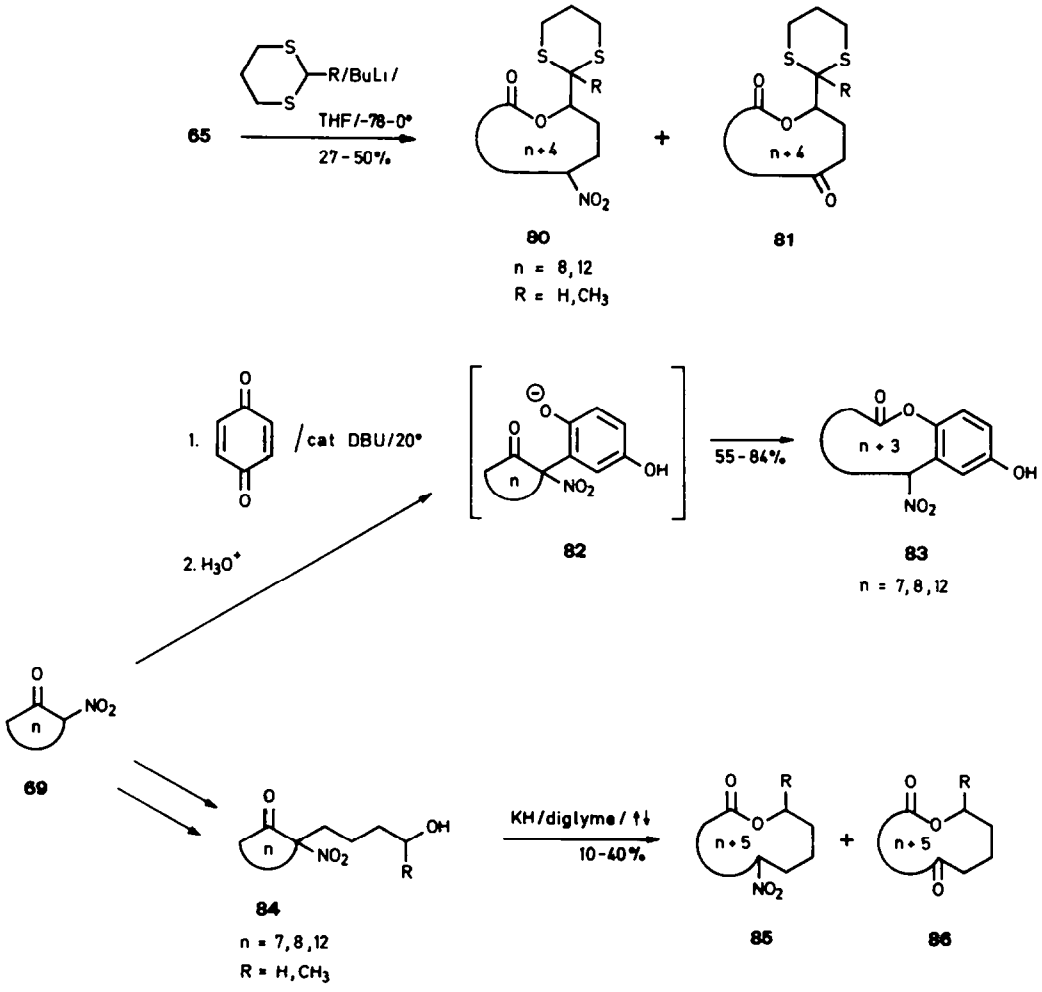
Alternatively the aldehydes **65** can be transformed to the alcohols of general formula **77** (Scheme 16) which can easily be rearranged to the lactones **79**. The primary alcohols (type **77**, R = H) have been prepared from **65** by reduction with $NaCNBH_3$ or with $NaBH_4$ in EtOH and rearranged in the presence of catalytic amounts of NaH in boiling diglyme.[64] The secondary alcohols (type **77**, R = CH_3) can be obtained by regioselective alkylation of the aldehyde function of **65** with $CH_3Ti[OCH(CH_3)_2]_3$ or $(CH_3)_2Ti[OCH(CH_3)_2]_2$[65] and rearranged with NaH/[18]crown-6/diglyme or with TBAF/THF.[27] Methylation of **65** (n = 6) led directly to the bicyclic intermediate **78** (n = 6, R = H), which is identical with **1**. Its structure has already been presented in Scheme 2 and no other diastereoisomers were found. Since there is strong evidence that methylation of **65** with the Ti-reagent is not diastereoselective, there should be an equilibrium of **77**, **78** and **79** during the aqueous work up of the reaction. The natural products[66] (±)-phoracantholide I, (±)-dihydrorecifeiolide and (±)-15-hexa-decanolide were synthesized in high overall yields by using this ring enlargement reaction as a key step.

Approaches to macrocyclic benzolactones have also been reported.[26] Treatment of **65** with lithio-



Scheme 16.

dithianes in THF affords directly a mixture of macrocyclic nitro- and oxo-lactones (**80** and **81**, Scheme 18).[58] The transformation of **69** to **83** (Scheme 17) is an example of the incorporation of three ring atoms. Reaction of 2-nitrocycloalkanones (**69**) with 1,4-benzoquinone gave directly the ring enlargement product **83**. From **69** (n = 6) no 9-membered benzolactone could be obtained.[67]



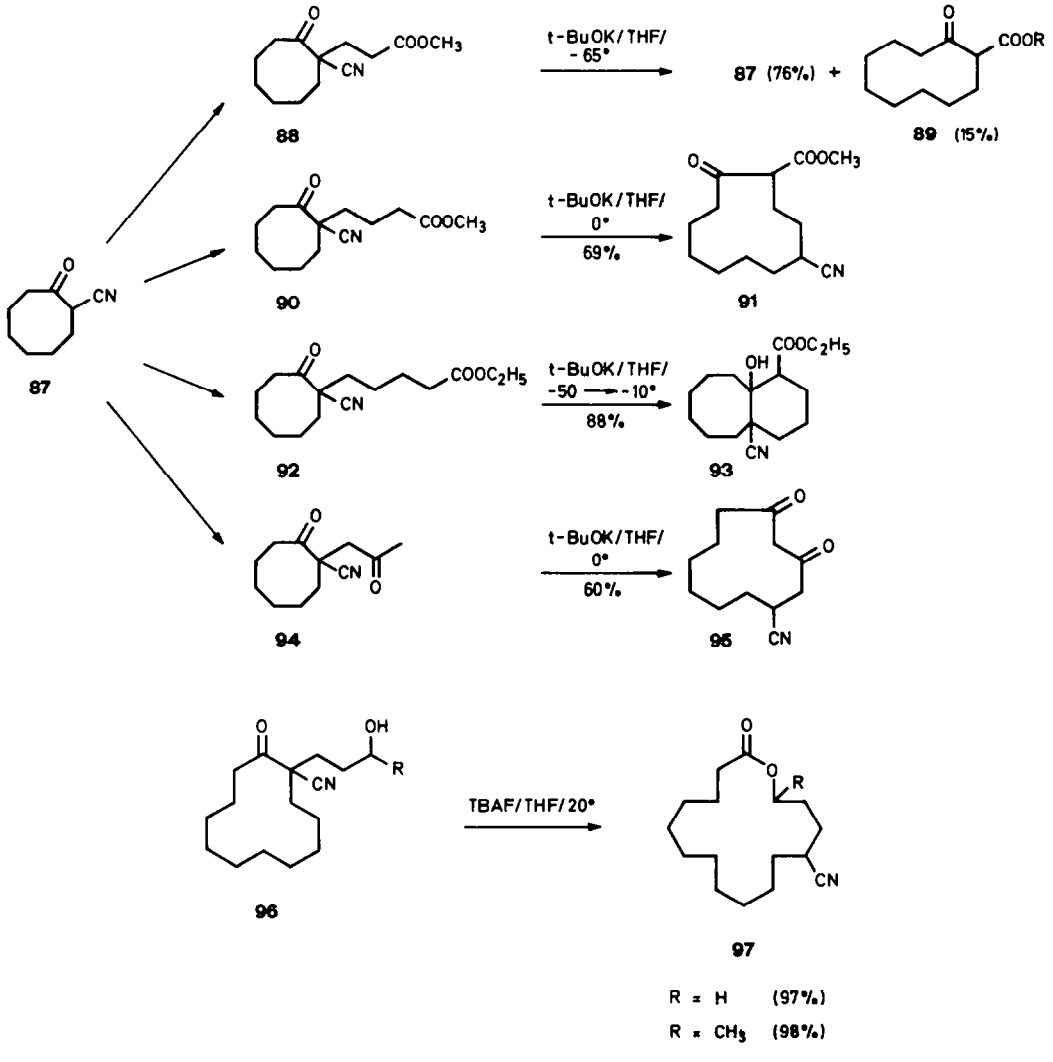
Scheme 17.

Starting from **84** (Scheme 17) ring expansions by five atoms are possible, although very drastic conditions are necessary (KH, boiling 1,2-dimethoxyethane, DME). Yields are generally low.

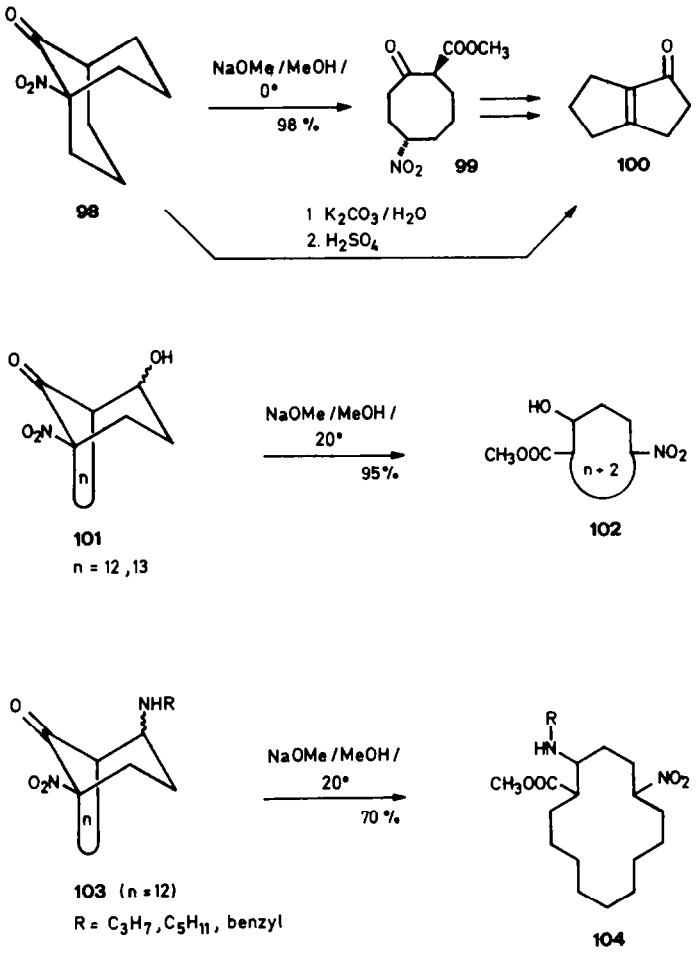
In summary it may be assumed that lactams are formed more easily than corresponding lactones and this is independent of the ring size and the number of atoms to be incorporated. When high temperature or strong basic conditions are necessary for the rearrangement, simultaneous Nef reaction may occur. This was particularly observed in some lactonization reactions.

6.4. 2-*Cyanocycloalkanones*

Derivatives of 2-cyanocycloalkanones may also be rearranged to macrocarbocycles[68,69] (Scheme 18). The course of the reaction is similar to that of the SO_2Ph- or NO_2-series. Two or three carbon atoms respectively can be incorporated by this method. Formation of **89** (15%) is accompanied by a retro-Michael reaction due to the highly basic reaction conditions. Compound **92** gave only the bicycle **93** whereas the compounds **90** and **94** rearranged in satisfactory yields. Under the same reaction conditions the 12-membered homologues of **88**, **90**, **92** and **94** led only to traces of the desired expanded rings. On the other hand, the corresponding lactonization reactions proceed in excellent yields (Scheme 18).[70] Introduction of the side chain in **96** (R = H, CH_3) is in principle accomplished in the same way as in the NO_2-series (see Section 6.3). Treatment of the alcohols **96** with catalytic amounts of TBAF, produced the lactones **97** (see also[71]).



Scheme 18.



Scheme 19.

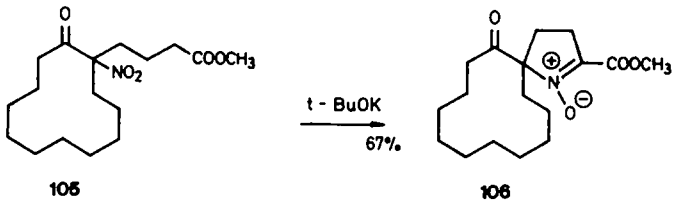
6.5. *Ring enlargement of bicyclic oxocarbocycles by attack of an external nucleophile*

As already shown (Section 6.3) 2-nitrocycloalkanones may undergo cleavage of the α-bond by reaction with external nucleophiles.[54] In an analogous manner the bicyclic compounds **98**, **101** and **103** can be transformed to ring enlarged products. Thus attack of CH_3O^- at the carbonyl carbon atom of **98** gave exclusively compound **99**.[72] Under the conditions of the $TiCl_3$ mediated Nef reaction, **99** leads directly to **100**. The latter can also be obtained by simply treating **98** with aqu. K_2CO_3 and H_2SO_4. In the same way the bicycles **101**[73] and **103**[74] have been transformed into the (n+2)-membered 1,2,5-functionalized macrocarbocycles **102** and **104** respectively.

The cleavage of the α-bond in **101** (n = 13) has been used for the preparation of the 15-membered starting material in the synthesis of the antibiotic A 26771B.[75]

6.6. *Discussion of the auxiliary groups* COR, SO_2R, NO_2 *and* CN

Under ideal circumstances the auxiliary group should be added to the 2-position of the cycloalkanones under mild conditions. It should then activate the 2-position for the introduction of the side chain, facilitate the heterolytic cleavage of the C(1)–C(2) bond and be easily removed, or at least transformed, after the ring enlargement has taken place. With respect to this criteria, the behavior of different auxiliary groups will be briefly discussed. The synthesis of 1,3-cycloalkandiones from cycloalkanones involves extensive preparative work.[76] The 2-cyanocycloalkanones are easier to prepare, but give only moderate yields[68] and moreover, they are very toxic. The introduction of NO_2-[54] and SO_2R-[77] groups is much simpler and the yields are good. The SO_2R- and CN-compounds are most adequate for the introduction of the side chain: beside the Michael reaction[53] and the Pd(O) catalyzed addition,[51] the reactions with alkyl halides[53,69] proceed in good yields. During the reaction of 1,3-diketones with alkyl halides O-alkylations can be observed frequently. Subsequent



105 106

Scheme 20.

transformations of functional groups in the side chain are in all cases problematic since the C(1)–C(2) bonds in the activated cycloalkanones are unstable against acid, base as well as external nucleophiles. The electron acceptor properties of the SO_2R- resp. NO_2-residues are both good enough to promote the ring enlargement reactions.[27,53] Elimination of $PhSO_2H$ might become a problem in certain rearrangements of phenylsulfonyl cycloalkanones. On the other hand the electrophilic nitrogen atom of 2-nitrocycloalkanones (**105**) can be attacked by an internal carbanion leading to nitrones (**106**) as shown in Scheme 20.[78] 2-Cyanoketones seem to be less suitable for C,C-rearrangements,[69] but show good results in lactonization reactions.[70,71] During C,C-rearrangements of cyano- and nitroketones the undesired retro-Michael reactions have sometimes been observed. Finally the removal or transformation of the auxiliary groups in the ring expansion product should be accomplished under mild conditions. In this respect the SO_2R-residue has great advantages since it can be reductively eliminated with $Na/Hg–Na_2HPO_4$[51,53,79] or by electrolysis[52,80] in excellent yields. The NO_2-group in contrast, is often removed stepwise by first converting it in an oxo group. Unfortunately most methods for this so called Nef reaction[81] are too drastic to be applied to the ring expanded products (especially lactones). Good results have been obtained with $TiCl_3/NaOAc$[61] or $KMnO_4$.[82] Afterwards the keto group can be removed via thioacetal hydrogenation[27,59] or via reduction of the corresponding tosylhydrazone.[67,83] Methods of direct reductive removal of the NO_2-residue have recently been reviewed.[84] Available procedures are normally limited to the reduction of tertiary or activated secondary nitro groups. However treatment of 6-nitro-9-decanolide,[27] containing an aliphatic secondary NO_2-residue, with Bu_3SnH led to (±)-phoracantholide I in 48% yield.[85] Degradation of a secondary CN-group is comparatively more difficult. One possibility is its reduction to CH_2-NH_2 followed by a Cope or Hofmann degradation sequence. The resulting exocyclic methylene group can then be ozonolized.[70] Direct removal of the CN-group by oxidative[86] or reductive[87] methods have also been reported. Beside the auxiliary groups already mentioned, other residues, such as CH_2-OTs or CH_2-NR_3^+, have been successfully employed in ring enlargement reactions.[88,89] In these cases OTs resp. NR_3^+ act as leaving groups. These transformations thus represent fragmentation reactions, which are not dealt with in this review.

The ring enlargement strategies discussed in this Tetrahedron Report seem to be useful synthetic alternatives for the preparation of macrocycles, if the method is chosen properly. The most suitable field of application are the syntheses of 10- to 16-membered carbocycles, lactams and lactones taking into account that the position and the type of substituents are restricted. Additionally the transamidation reactions as well as combinations of different ring enlargement strategies are very suitable for the synthesis of polyamine alkaloids.

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