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Substituted Cyclobutenes, Their Preparation, and Their Versatility in Synthesis

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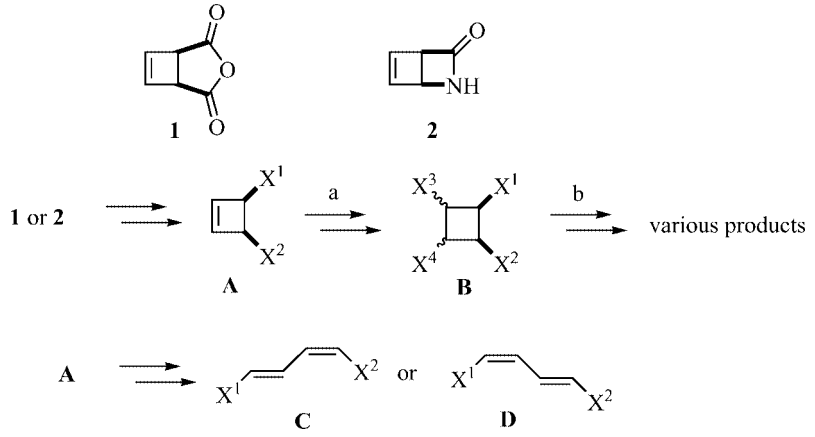
Cyclobutene compounds are interesting intermediates that have proven to be useful in organic synthesis. This review mainly deals with preparations and reactions of some cyclobutenes disubstituted at the allylic position. Several possibilities in the area of the thermal ring opening of these compounds into dienes are explored, and some features of the selectivity of addition reactions to cyclobutenes to afford tri- or tetrasubstituted cyclobutanes are also examined. When suitable leaving groups are present, these cyclobutanes can yield cyclopropanes stereospecifically through ring contraction or bicyclic compounds through intramolecular cyclization. Some applications to the synthesis of nucleoside analogues and of bicyclic compounds are pointed out.

Introduction

Numerous preparations of cyclobutene compounds disubstituted at the allylic positions (**A**) can be achieved. This review mainly covers the use of *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride (**1**) or 2-azabicyclo[2.2.0]hex-5-en-3-one (**2**) as the starting materials (Scheme 1). Compounds **A** bearing two substituents X^1 and X^2 can be obtained from **1** by various routes, whilst additions onto the double bond provide compounds **B**, which are useful intermediates, particularly for synthesis of nucleoside analogues and of some nitrogen bicyclic compounds by pathways involving inter- or intramolecular substitution or ring contraction. These compounds **A** can also be used in the synthesis of dienes **C** and **D** by electrocyclic ring opening.



Scheme 1. Reactions from cyclobutenes: a) addition only, or addition followed by another treatment, and b) several steps including substitution, ring contraction, or intramolecular cyclization.

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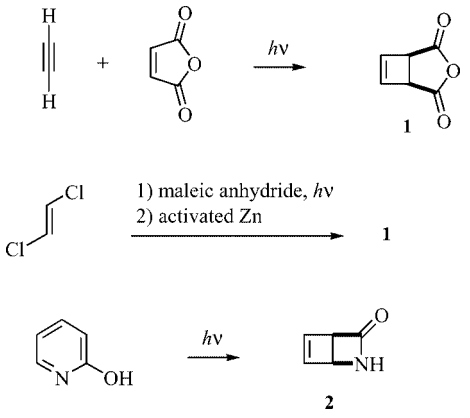
Synthesis of Several Cyclobutene Compounds

cis-Cyclobut-3-ene-1,2-dicarboxylic anhydride (**1**) is one of the most useful cyclobutene starting materials. It is available by photochemical [2+2] cycloaddition between maleic anhydride and acetylene,[1] whilst more recently[2] a method using (*Z*+*E*)- or (*E*)-dichloroethene[3] as acetylene equivalents has been developed. In the latter case the photochemi-

cal step is safer and less cumbersome, with subsequent elimination in the presence of activated zinc providing **1**, whilst the overall yield is comparable to that of the single-step procedure. A similar photocycloaddition with (*Z*)-dichloroethene and subsequent reductive dehalogenation has also been used to prepare lactonic cyclobutene compounds.[4]

Several trisubstituted cyclobutene compounds have been prepared by another two-step method involving thermal [2+2] cycloaddition between an enamine and dimethyl fumarate, followed by Hoffmann elimination,[5] whilst photochemical electrocyclic reactions have been used to prepare compounds such as 2-azabicyclo[2.2.0]hex-5-en-3-one (**2**), which is thus available from 2-hydroxypyridine[6] (Scheme 2).



Scheme 2. Synthesis of two useful starting materials.

Reduction of **1** with $LiAlH_4$ gave diol **3a**[1b,1d,7] (Figure 1), which could subsequently be benzylated[1d,7,8] or tosylated[1b] to provide **3b** and **3c**, respectively. Monoalkylation afforded **3d**[9] and **3e**,[10] whilst further reduction of **3c** yielded hydrocarbon **4**.[1b,9] Mild reduction of **1** with $NaBH_4$ gave lactone **5**,[9] which was also obtained by Wallace et al. by oxidation of **3a**.[11] The enzymatic acylation of **3a** in the presence of *Pseudomonas fluorescens* lipase predominantly yielded monoacetate (–)-**6**,[12] and the enantiomeric excess was increased when this reaction was carried out below room temperature.[13] The other enantiomer (+)-**6** was available by diacetylation of **3a** and subsequent hydrolysis in the presence of the same enzyme.[14a] Enzymatic hydrolysis of the same diacetate in the presence of porcine pancreatic lipase has also been carried out,[14b] the monoacetates being used for the synthesis of both enantiomers of lactone **5**.[12] One of these enantiomers was also available by enzymatic oxidation of diol **3a**.[15] Diesters and monoesters **7**–**8** were prepared from **1** either as racemates[1d,8,16,17] or – for (+)-8 – as the nonracemate.[14a,18] In the case of **7c** an alternative route from 1,3,5,7-cyclooctatetraene has been proposed.[19] Further isomerization of (+)-**8** provided (+)-**9**.[18] Diols (+)-**10**, (+)-**11**, (+)-**12** and (+)-**13** have been obtained from monoacetate (–)-**6**[20] by several routes, involving an epimerization step in each of the last three cases (Figure 1).

Noëlle Gauvry, born in 1972 in France, graduated from the Ecole Nationale Supérieure de Chimie de Clermont Ferrand. She obtained her Ph.D. in 1999 under the guidance of Prof. F. Huet at the University of Le Mans, working on the synthesis of carbocyclic nucleoside analogues. After a year as an assistant professor with Prof. J. Mortier in Le Mans, she joined the group of Prof. P. D. Magnus at the University of Texas at Austin as a postdoctoral fellow in 2000. Since 2002 she has been working as a lab head for Novartis Animal Health in Basle, Switzerland. Her research interests are focused on the discovery of new antiparasitic drugs.

Cyrille Lescop was born in 1972 in France and graduated from the Ecole Nationale Supérieure de Chimie de Clermont Ferrand in 1995. He completed his Ph.D. (2000) in the group of Prof. F. Huet at the University of Le Mans on the synthesis of bicyclic amino acids and nucleosides. He then worked as a postdoctoral fellow with Prof. P.D. Magnus at the University of Texas at Austin. In 2002 he joined Santhera Pharmaceuticals (formerly MyoContract), a Swiss biopharmaceutical company located in the Basle area. As a medicinal chemist, he has been involved in the discovery of new therapeutics for neuromuscular diseases.

François Huet was born in 1942 in France. He obtained his Ph.D. degree in 1969 at the University of Paris XI Orsay under the supervision of Professor P. Fréon, and he joined the group of Professor H. Favre at the University of Montreal for a 16 month postdoctoral period. He returned to Orsay and then in 1988 joined the University of Le Mans, where he is currently Professor. His present research interests are mainly focused on synthesis of cyclic and acyclic nucleoside analogues, lactones, and other compounds with potential biological properties.

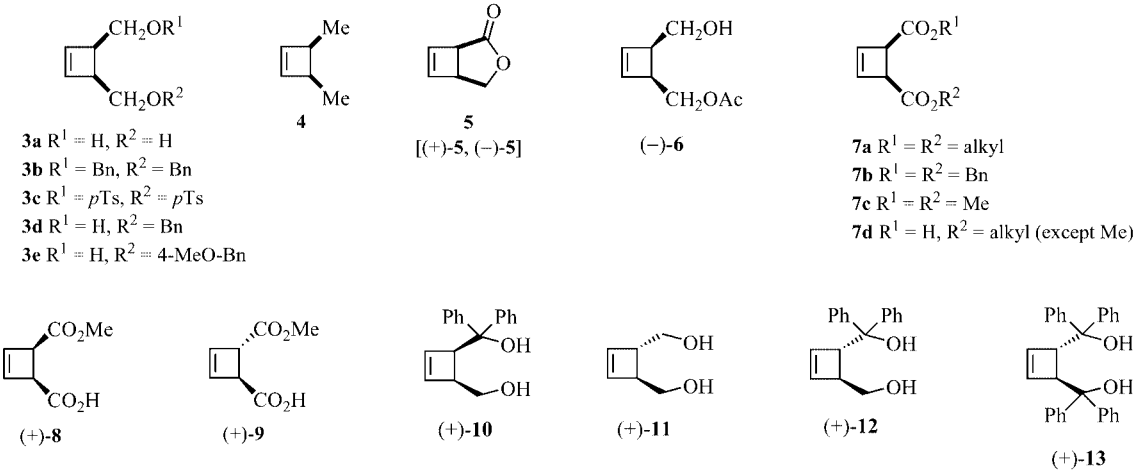
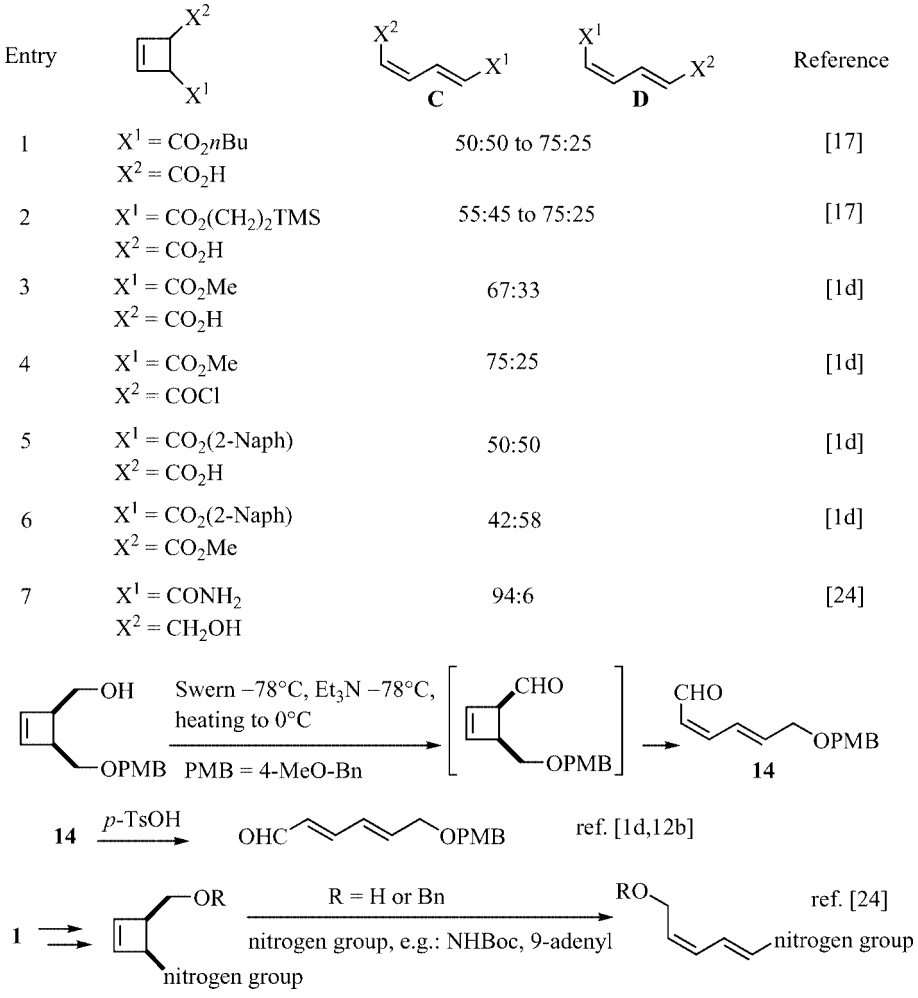


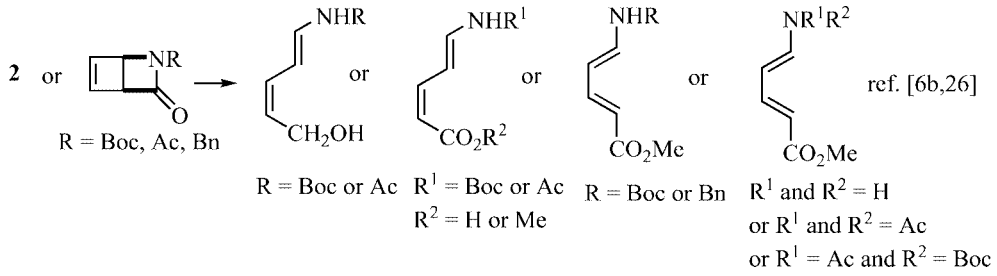
Figure 1. Cyclobutene compounds obtained from **1**.

Synthesis of Dissymmetrical Dienes

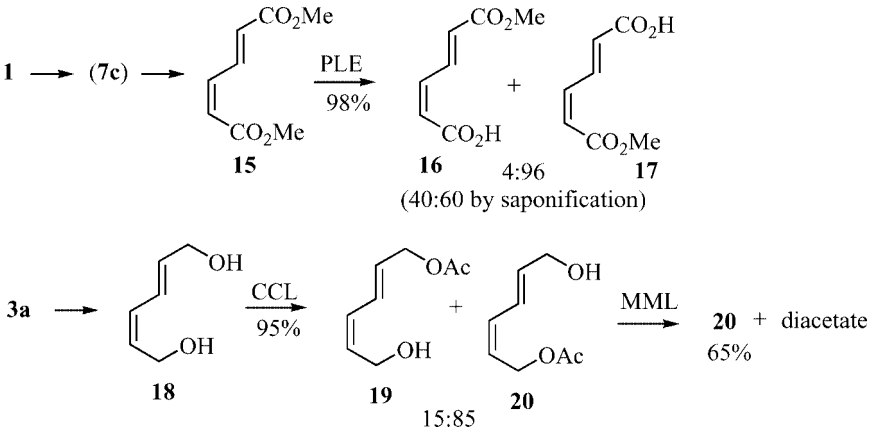
Thermal ring opening of cyclobutene compounds disubstituted at the allylic position provides dienes. As would be anticipated from symmetry rules,[21] the *cis*-compounds **A** usually produce mixtures of both (*Z,E*)-dienes **C** and **D** (Scheme 1), though the ratio strongly depends on the natures of the substituents. On the other hand, subsequent isomerization to (*E,E*) products may occur. Several examples of such openings are given in Scheme 3.



Scheme 3. Ring opening of cyclobutenes.



Scheme 4. Dienic nitrogen compounds.



Scheme 5. Enzymatic reactions with dienes.

Trost et al. showed in the case of several diacid monoesters (Entries 1 and 2) that the selectivity depends on the experimental conditions. The results were interpreted by making allowance for the hydrogen bonding between the CO_2H group and DMSO when this solvent is used. This would increase the effective bulk of this substituent, resulting in its preferential outward rotation, in contrast to reactions carried out in CCl_4 or CH_2ClCH_2Cl. Influence of secondary orbital interactions was also envisioned.[17] Over the years it became evident that numerous results could not be interpreted only in terms of steric effects, and theoretical works on these ring openings by Houk's group[22] showed that orbital interactions within the transition state tend to favor outward rotation in the case of π-donor groups and inward rotation in the case of π-acceptor substituents.

This hypothesis is consistent with a diminution in the inward rotation preference when the π-acceptor character of the substituent decreases [COCl > CO_2H ≈ CO_2(2-Naph) > CO_2Me].[1d,23] Another withdrawing substituent, the amide group, gave good selectivity.[24]

In several cases, ring opening has even provided only one diene; in the case of the CHO group, for instance, an exclusive inward rotation was observed.[1d,10,11,12b,25] In contrast, nitrogen groups exclusively gave outward rotation.[24] Examples of the further isomerization of the primary diene (e.g., **14**) to give the (*E*,*E*) product have been reported.[1d,12b]

Several dienic nitrogen compounds were also available through the opening of lactam **2** or its derivatives.[6b,26] These results confirmed the outward rotation preference of nitrogen groups and the possibility, in some cases, of subsequent isomerization to the (*E*,*E*)-dienes (Scheme 4).

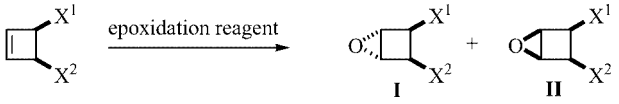
Enzymatic reactions with dienes obtained by thermal opening of cyclobutene compounds gave good results (Scheme 5). Whilst the dienic diester **15** displayed poor selectivity in partial saponification with KOH, hydrolysis in the presence of pig liver esterase resulted in a pronounced predominance of isomer **17**.[27] Enzymatic acetylation of diol **18** also proved to be selective, and monoacetate **20** was the major product when the reaction was carried out in the presence of *Candida cylindracea* lipase, though it was not possible to separate it from the minor isomer **19**. Fortunately, however, when the **19** + **20** mixture was acetylated in the presence of an enzyme with inverse selectivity, the lipase of *Rhizomucor mihei*, the minor isomer was acetylated and compound **20** was isolated in satisfactory yield.[28]

Various Addition Reactions

Various addition reactions to cyclobutene derivatives have been investigated. Bromine addition,[29] catalytic hydrogenation,[30] and catalytic deuteration[31] involving anhydride **1** and catalytic hydrogenation of (–)-**6**[13] and of **5**[32] gave the expected products in high yields. In the case of the catalytic deuteration the major product was the *exo* isomer (≥96%).

Epoxidation of cyclobutenes disubstituted at the allylic positions has been examined. With electron-withdrawing substituents, reaction with *m*CPBA was very slow[9]

Table 1. Examples of epoxidations of cyclobutene compounds.

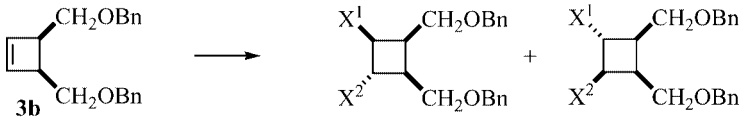


Entry	X^1, X^2	Reagent, conditions[a]	Yield (%)	**I/II** ratio	Ref.
1	$X^1 = X^2 = CO_2Me$	A, 3 d	≈ 40[b]	86:14	[9]
2	X^1, $X^2 = COOCH_2$ (lactone)	A, 5 d	89	81:19	[9]
3	$X^1 = X^2 = CH_2OH$	A, 15 h	90	17:83	[9]
4	$X^1 = X^2 = CH_2OH$	B, 5 h	80	33:67	[34]
5	$X^1 = CH_2OH$, $X_2 = CH_2OBn$	A, 15 h	76	22:78	[9]
6	$X^1 = X^2 = CH_2OMs$	B, 12 h	99	10:90	[34]
7	$X^1 = X^2 = CH_2OMs$	C, 5 h	85	21:79	[34]
8	$X^1 = X^2 = CH_2OMs$	A, 18 h	69	13:87	[34]
9	$X^1 = X^2 = CH_2OMe$	B, 10 h	99	38:62	[34]
10	$X^1 = X^2 = CH_2OBn$	A, 8 h	91	28:72	[9]
11	$X^1 = X^2 = CH_2OBn$	D, 8 d	69[c]	72:28	[9]
12	X^1, $X^2 = CH_2OS(O)OCH_2$[d]	B, 12 h	85	30:70	[34]

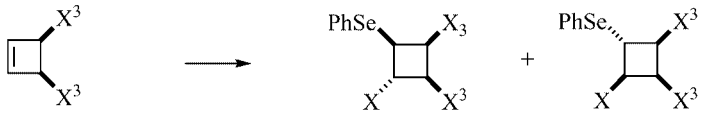
[a] A: *m*CPBA, CH_2Cl_2, room temp. B: dimethyldioxirane (DMD), CCl_4/acetone 9:1, room temp. C: DMD, acetone, room temp. D: Payne's reagent (PhCN, 30% H_2O_2), room temp. [b] More than 50% of starting material recovered. [c] 7% of starting material recovered. [d] One of the diastereomers with respect to sulfur configuration (the other exclusively gave the *anti* product).

(Table 1, Entries 1 and 2), but the results were satisfactory in the case of the compound with a lactone moiety. These reactions mainly proceeded from the less hindered side. When the substituents were hydroxymethyl groups (Table 1, Entry 3), epoxidation with *m*CPBA mainly provided the *syn* product,[9] probably as a result of hydrogen bonding between these hydroxy groups and an oxygen of the peracid.[33] Treatment of the same compound with dimethyldioxirane (DMD) also showed a preference for the *syn* product (Entry 4),[34] as did treatment of a monohydroxylated compound with *m*CPBA (Entry 5). Results from oxygenated compounds without hydroxy groups were more surprising. These also displayed a predominance of the *syn* products (Entries 6–10, 12), but the selectivity was reversed when the oxidant was Payne's reagent (Entry 11). In the case of DMD, replacement of acetone as solvent by a less polar mixture (CCl_4/acetone 9:1) often produced a decrease in the rate and an increase in the *syn*/*anti* ratio. These *syn* preferences were carefully examined in the experimental and theoretical work of Freccero et al.,[34] in which the predominant *syn* facial selectivity was interpreted as mostly the result of an electrostatic attractive interaction involving the peroxy oxygens of the oxidizing reagents and the positively charged homoallylic hydrogen atoms of the olefins.

In the case of bromohydroxylation of 3,4-bis(benzyloxymethyl)cyclobut-1-ene (**3b**, Scheme 6) the major product was the result of a *syn* preference for the electrophilic attack (Entry 1).[9,35] A *syn* selectivity was also observed in the



Entry			
1	a: X^1 = Br, X^2 = OH, 75%	90:10	ref. [9,35]
2	b: X^1 = SePh, X^2 = Cl, 82%	94:6	ref. [9]
3	c: X^1 = SePh, X^2 = Br, 82%	95:5	ref. [9]
4	d: X^1 =OH, X^2 = H, 93%	13:87	ref. [38a]



Entry			
5	b: $X^3 = CO_2Me$, X = Cl, 94%	92:8	ref. [9]
6	c: $X^3 = CO_2Me$, X = Br, 93%	>95:5	ref. [9]
7	c: $X^3 = CH_2OH$, X = Br, 70%	86:14	ref. [9)
8	c: $X^3 = CH_2NHBoc$, X = Br, 86%	85:15	ref. [36]

Scheme 6. Additions to cyclobutene compounds: a) NBS, moist DMSO, 10 °C then room temp., b) PhSeCl, CH_2Cl_2, room temp., c) PhSeBr, CH_2Cl_2, room temp., d) BH_3, THF, room temp. then 30% H_2O_2, 50 °C.

course of haloselenylation[9,36] of cyclobutenes with substituents including oxygen or nitrogen atoms (Entries 2, 3, 5–8). This preference is likely to be due to stabilization of the intermediary selenonium ion by the lone pairs of these atoms.[37] The reaction with the dissymmetrical compound **3d** also proceeded with *syn* selectivity but was not regioselective, whilst that with lactone **5** was also not regioselective, with *anti* attack being predominant in this case, as in the course of epoxidation.[9] As would be expected, hydroboration mainly occurred from the less crowded sides of several cyclobutenes (e.g., Entry 4).[38]

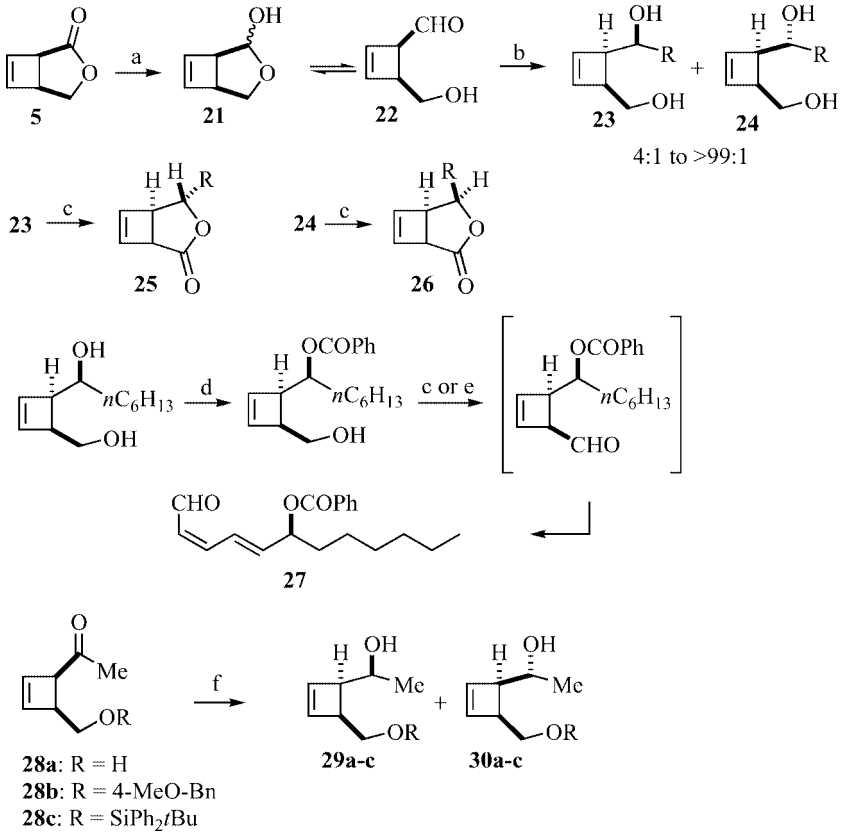
Addition of Organometallic Reagents to Lactol 21 and Reduction of Ketones 28a–c (refs.[11,12b])

Lactol **21**, existing in equilibrium with aldehyde **22**, was generated in situ by reduction of lactone **5** at –78 °C. Addition of an organometallic reagent [MeLi, MeMgBr with or without $ZnBr_2$ as additive, $MeTi(OiPr)_3$, RMgBr (R = Et, *n*Pr, *n*Bu, *n*Hex)] at this temperature, followed by warming of the reaction mixture (1 h at 20 °C), provided a mixture of the two addition products **23** and **24** (Scheme 7). The major diol was isomer **23** and the highest selectivity was observed in the case of $MeTi(OiPr)_3$ (the relative stereochemical relationships were established after oxidation of the isolated diols to the corresponding lactones **25** and **26**). An interesting application for one of these diols was the preparation of diene **27**, an intermediate for the synthesis of arachidonic acid, previously obtained by another group by a different route.[39] The methodology could be developed to prepare dienals such as **27** with stereocontrol, as lactone **5** is available in both enantiomeric forms.[12,15]

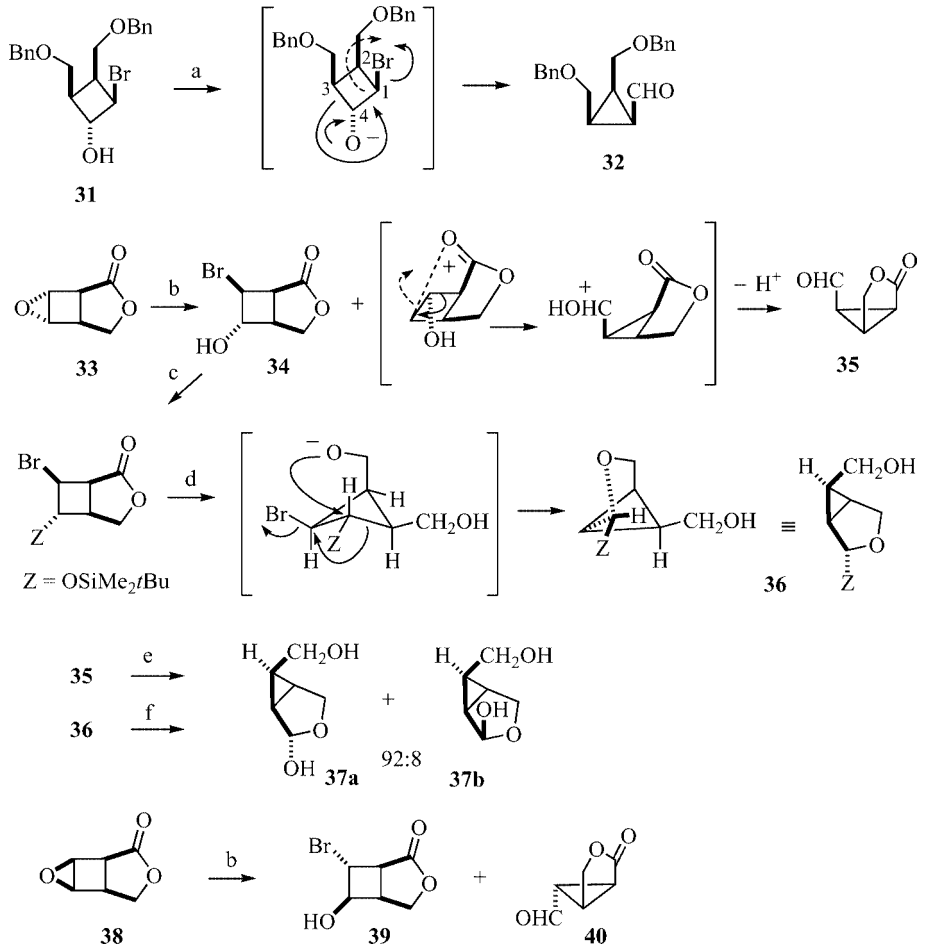
Reduction of ketones **28a–c** with various hydrides provided the corresponding alcohols **29a–c** and **30a–c**, with the major products being the alcohols **29a–c**. The diastereoselectivity in the course of this reaction with respect to the nature of the reducing agent was investigated.

Ring Contraction

Several compounds resulting from addition to cyclobutene compounds gave ring contraction products in acidic or basic media; some monocyclic and bicyclic cyclopropane compounds in this area are illustrated in Scheme 8. When the major bromohydroxylation product of 3,4-bis(benzyloxymethyl)cyclobut-1-ene – compound **31** – was subjected to treatment with sodium hydroxide, a ring contraction to afford aldehyde **32** took place.[9,35] A mechanistic hypothesis involving breaking of the bond between C-3 and C-4 and a nucleophilic attack *anti* to bromine could explain the isolation of this compound as the sole isomer. The aldehyde with a *trans* relationship between the CHO group and both benzyloxymethyl groups was available from the minor



Scheme 7. Additions to lactol **21** and to ketones **28a–c**: a) DIBAH, THF, hexanes, –78 °C. b) R–M (see text). c) Tetrapropylammonium perruthenate, 4-methylmorpholine *N*-oxide, 4-Å mol. sieves, CH_2Cl_2, 25 °C. d) 1) NaH, THF, 4-MeO-C_6H_4-CH_2Br, 2) PhCOCl, pyridine, 3) DDQ, CH_2Cl_2. e) Oxalyl chloride, DMSO, CH_2Cl_2, –78 °C. f) Various hydrides.



Scheme 8. Ring contraction: a) NaOH, toluene, room temp., 24 h. b) 48% HBr, acetone, room temp. 7 h. c) tBuMe$_2$SiCl, imidazole, THF. d) LiEt$_3$BH (5 mol-equiv.), THF reflux, 5 d. e) DIBAH, THF, –78 °C. f) nBu$_4$NF, THF, 5 h, room temp.

bromohydrin. Analogous ring contractions affording cyclopropane compounds had already been observed.[40]

Other cyclopropanes were available from compound **33**,[38a,41] the major epoxidation product obtained from lactone **5**, which on treatment with hydrobromic acid provided a mixture of bromohydrin **34** and aldehyde **35**, the latter compound probably formed via an intermediate carbonium ion stabilized by anchimeric assistance of the vicinal carbonyl group. As for bromohydrin **34**, it mainly remained unchanged in this mixture. Unexpectedly, after silylation of **34** and subsequent treatment with superhydride for several days, the bicyclic alcohol **36** was obtained. This new ring contraction was explained in terms of a nucleophilic attack on the carbon bearing the silylated group, breaking of the vicinal C–C bond, and nucleophilic attack *anti* to bromine. Compound **36** was thus isolated as a unique isomer. Reduction of **35** or desilylation of **36** provided the same epimeric mixture of **37a** and **37b**. Finally, once these two possibilities had been taken into account, the **37a** + **37b** mixture was obtained in satisfactory yield from **33**. Similarly, the other isomer **38** afforded a mixture of bromohydrin **39** and aldehyde **40**.

Other Reactions

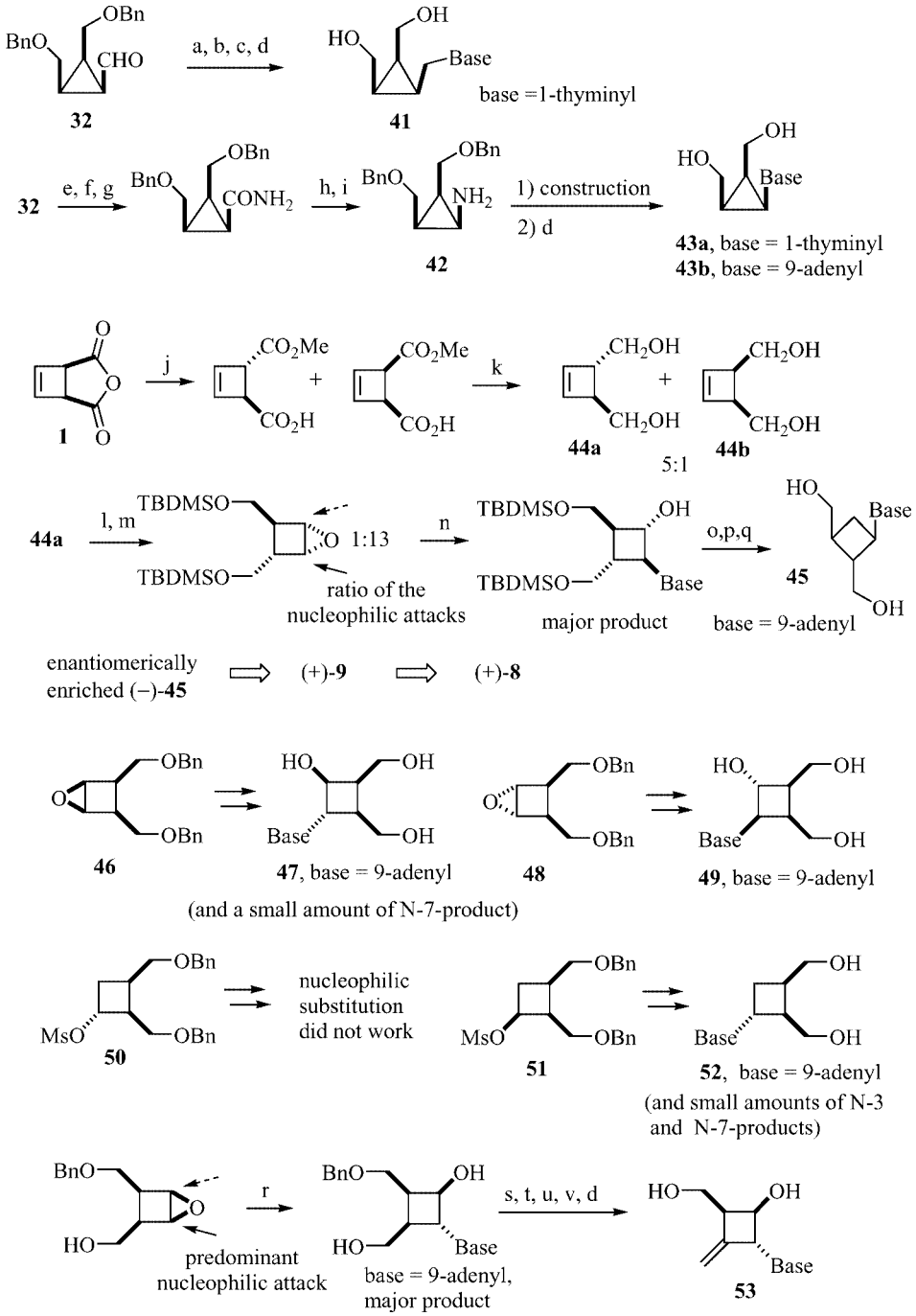
Anhydride **1** has also found interesting applications not fully covered in this review, having been used, for instance, together with other cyclobutene precursors, to generate cyclopentadiene by photolysis[42] and cyclopentadienone by photolysis or pyrolysis,[43] as a dienophile in Diels–Alder reactions,[44] or as an acetylene equivalent in both 1,3-dipolar and Diels–Alder cycloadditions.[45] It has also served as a precursor of 3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide, which provided seven-membered ring systems by SO_2 extrusion followed by Cope rearrangement of the resulting *cis*-1,2-divinyl intermediate.[46]

Application to the Synthesis of Monocyclic, Bicyclic, and Acyclic Nucleoside Analogues

Several cyclobutenes and products derived from cyclobutenes have been used in syntheses of nucleoside analogues, especially of compounds with structural analogies with carbovir (or its prodrug abacavir) or oxetanocin. This review only covers the synthetic aspects.

A number of cyclopropane nucleosides were obtained from compound **32** (Scheme 9), the synthesis of one of them – compound **41** – being carried out by a route involving a substitution step, reduction, mesylation, treatment with thymine, and debenzylation to provide the desired compound.[35] In the cases of compounds **43a** and **43b**, the syntheses were based on construction of thymine or adenine, respectively, after the production of amine **42**. Subsequent debenzylation provided these two sterically hindered nucleosides in satisfactory overall yields.[47]

Syntheses of racemic and enantiomerically enriched cyclobut-A (**45**) and of analogues have been investigated.[18] In the racemic approach, treatment of anhydride **1** with methanol in basic medium yielded a mixture of both expected hemiesters, with a predominance of the *trans* form. Reduction provided an easily separable mixture of alcohols

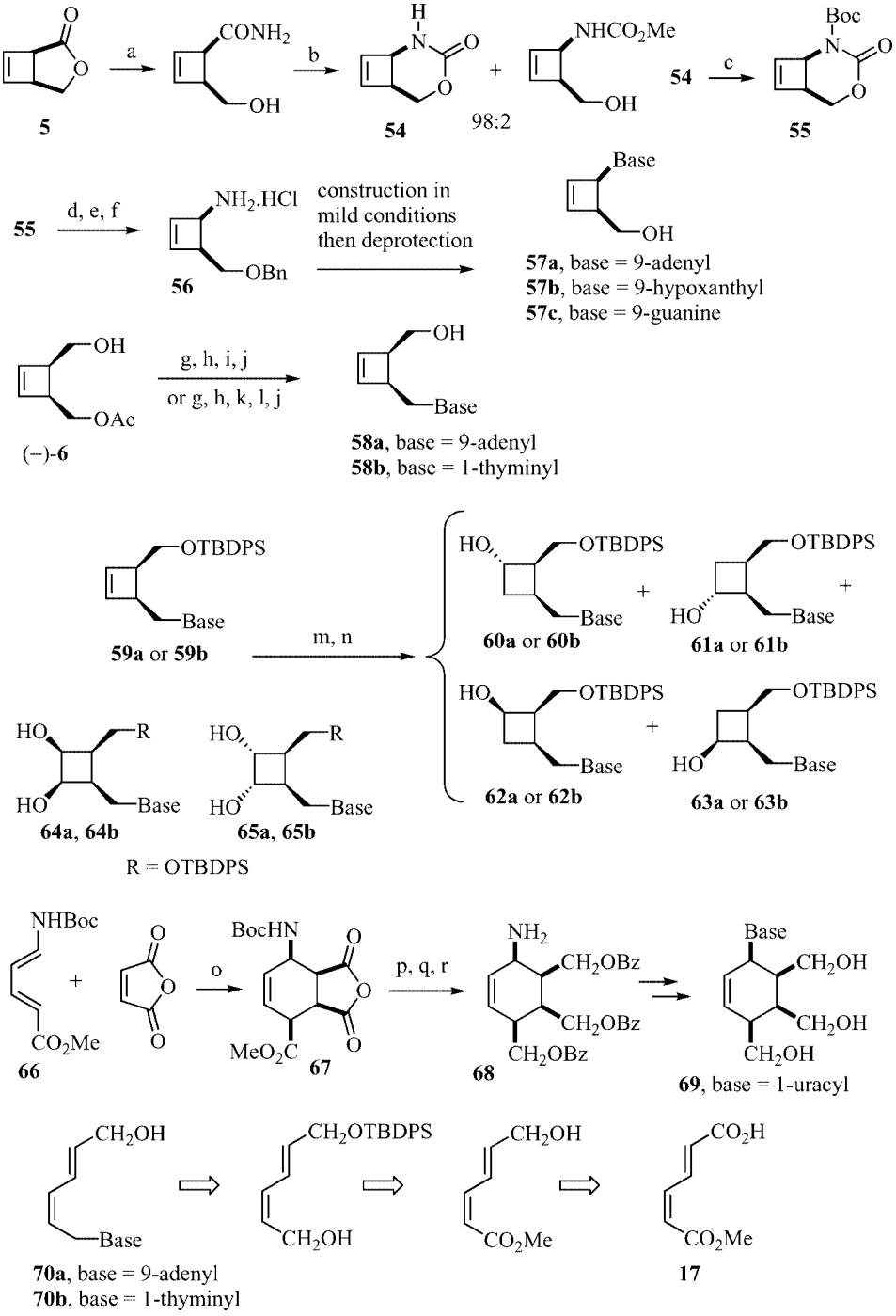


Scheme 9. Synthesis of cyclopropane and cyclobutane nucleoside analogues: a) $NaBH_4$, Et_2O, 0 °C. b) MsCl, Et_3N, CH_2Cl_2, 0 °C. c) Thymine, K_2CO_3, 18-crown-6, nBu$_4$NHSO$_4$, DMSO, room temp., 20 h. d) BCl_3, CH_2Cl_2, –78 °C. e) Jones' reagent. f) $ClCO_2Et$, Et_3N. g) NH_3. h) $PhI(OAc)_2$. i) KOH. j) NaOMe, MeOH. k) $LiAlH_4$. l) tBuMe$_2$SiCl, imidazole, DMF. m) mCPBA, CH_2Cl_2. n) NaH, adenine, DMSO, 18-crown-6, 114 °C. o) PhOCSCl, 4-DMAP, MeCN. p) nBu$_3$SnH, AIBN. q) AcOH, H_2O, 90 °C. r) Adenine, DBU, DMF, 110 °C. s) BnBr, NaH, DMF. t) MsCl, Et_3N, DMAP, CH_2Cl_2. u) oNO$_2$C$_6$H$_4$SeCN, $NaBH_4$, EtOH, v) H_2O_2, THF.

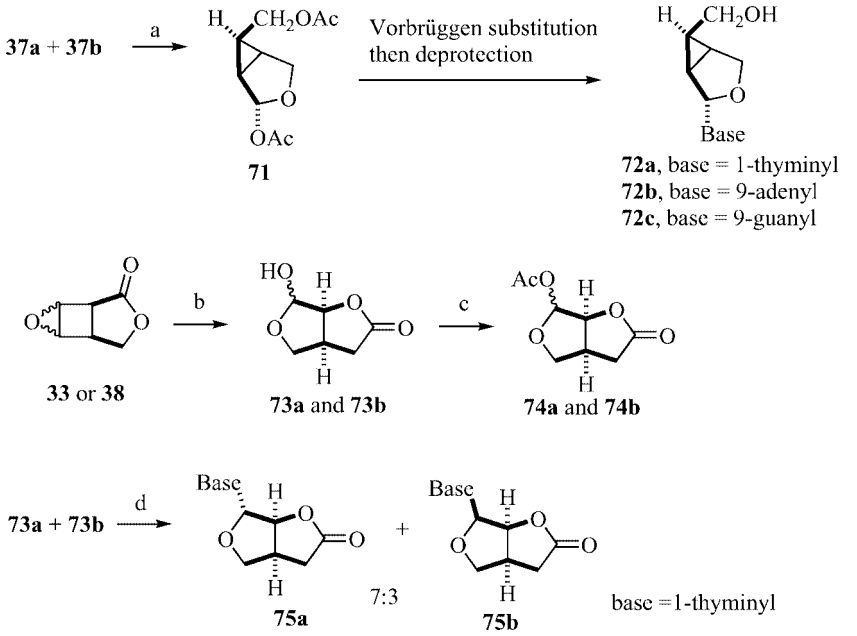
44a and **44b**. After silylation and subsequent epoxidation of the major isomer **44a**, nucleophilic attack by adenine proceeded mainly from the less hindered side. The target molecule **45** was then obtained after removal of the hydroxy group by a radical method, followed by desilylation. The optically active product (–)-**45** was obtained from (+)-**9**.

Several syntheses also based on nucleophilic attacks on epoxides (**46** and **48**) provided tetrasubstituted nucleosides **47** and **49**.[7]

Mesylates **50** and **51** were obtained from alcohols produced by hydroboration of *cis*-3,4-bis(benzyloxymethyl)cyclobut-1-ene (**3b**) followed by oxidative treatment. Com-



Scheme 10. Synthesis of cyclobutene (and cyclobutane derivatives), cyclohexane, and dienic nucleoside analogues: a) NH_3, MeOH. b) $PhI(OAc)_2$. c) Boc_2O. d) LiOH, –10 °C. e) HCl, MeOH, ca. 0 °C. f) BnBr. g) *t*$BuPh_2SiCl$, imidazole, DMF. h) NH_3, MeOH. i) PPh_3, DEAD, adenine, THF. j) *n*Bu_4NF, THF. k) PPh_3, DEAD, *N*-3-benzoylthymine. l) NaOH. m) BH_3, THF. n) H_2O_2, NaOH. o) $CHCl_3$, reflux. p) $LiAlH_4$, THF. q) BzCl, pyridine, CH_2Cl_2. r) CF_3CO_2H, CH_2Cl_2.



Scheme 11. Synthesis of bicyclic nucleosides: a) Ac_2O, pyridine. b) H_2O + various acids. c) Ac_2O, pyridine, DMAP. d) Thymine + BSA, then addition to **73** + TMSOTf.

pound **50**, derived from the major hydroboration product, did not give the substitution product with adenine but underwent an unexpected ring contraction.[38a] In contrast, nucleophilic attack with **51** was easier, probably for steric reasons, and compound **52** was obtained after removal of the protecting groups.

The methylenecyclobutane nucleoside **53** was prepared from the major epoxidation product of **3d**. Treatment of this dissymmetrical epoxide with adenine provided several compounds, although the predominant attack occurred next to the hydroxymethyl group, probably due to intramolecular hydrogen bonding. Unexpectedly, it was then found that benzylation occurred selectively at the secondary hydroxy group. Compound **53** was then obtained by mesylation of the primary hydroxy group, substitution with a selenyl group, oxidation, and removal of the protecting groups.[48]

The synthesis of norcarbovir and analogues was achieved starting from lactone **5**[49] (Scheme 10), with compound **54** acting as an important intermediate. Opening of the carbamate moiety in this compound was not possible, but use of its Boc derivative **55** gave good results, providing hydrochloride **56** in three steps. Further elaboration under mild conditions, to reduce unwanted opening into dienes, followed by deprotection, gave the target molecules **57a**–**c**.

Analogues **58a** and **58b**, with methylene spacers, were available in enantiomerically enriched form from monoacetate (–)-**6**. In this case the strategy was based on a nucleophilic substitution under Mitsunobu conditions, which proved to be very efficient for avoiding the minor substitution products.[50]

Trisubstituted and tetrasubstituted products **60**–**65** were synthesized from the silyl derivatives of **58a** and **58b**, **59a**, and **59b** by hydroboration or dihydroxylation steps. Several nucleoside analogues were then obtained after removal of the protecting groups.[38c]

As dienes such as **66** were available from lactam **2**, their potential in Diels–Alder reactions was examined and the *endo* compound **67** was obtained in excellent yield. Preparation of the tribenzoate **68** by conventional means, construction of the uracil component, and subsequent debenzoylation provided the cyclohexene nucleoside **69**.[6b]

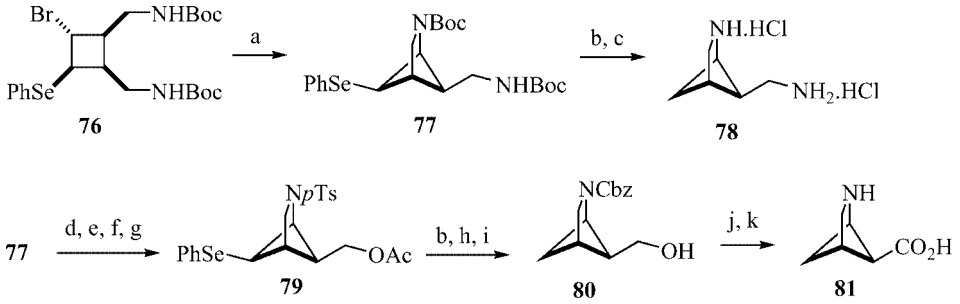
Two dienic nucleosides **70a** and **70b** were also prepared.[51] The starting material was the hemiester **17** and the strategy was based on the use of a Mitsunobu reaction to incorporate the base moiety.

Diols **37a** and **37b**, obtained from **33** by two different ring contractions, were used as precursors for the synthesis of bicyclic nucleosides **72a**–**c** by Vorbrüggen substitution followed by deprotection[41] (Scheme 11).

Other bicyclic compounds were obtained from the epoxidation products, **33** and **38**, of lactone **5**.[52] Acidic treatment resulted in a surprising rearrangement, with the bicyclic compound **73** being obtained in both anomeric forms. A mechanism involving opening of the intermediate cyclobutane diol and subsequent translactonization and hemiacetalization was proposed. Acetylation followed by coupling of thymine under Vorbrüggen conditions provided compounds **75a** and **75b**.

Application to the Synthesis of 2-Azabicyclo[2.1.1]hexanes

Compound **76** was easily available by haloselenylation (Scheme 6, Entry 8), and cyclization to provide the 2-azabicyclo[2.1.1]hexane derivative **77** was achieved in basic medium[36] (Scheme 12). Removal of the selenyl group by a radical method, followed by acidic treatment, provided dihydrochloride **78**.



Scheme 12. Synthesis of 2-azabicyclo[2.1.1]hexanes: a) NaH, DMF. b) nBu$_3$SnH, AIBN, toluene. c) HCl, MeOH. d) CF_3CO_2H, CH_2Cl_2. e) pTsCl, Et_3N, CH_2Cl_2. f) pTsCl, NaH, DMF. g) KOAc, KI, HMPA, 120 °C. h) 32% HBr, AcOH, EtOAc. i) CbzCl, 1 M NaOH, dioxane. j) CrO_3, H_2SO_4, acetone, –5 °C. k) H_2, Pd/C, MeOH.

Compound **77** was also converted into **79** by a sequence involving a nucleophilic attack of KOAc on a bis(tosylamino) group as the key step. The protected β-amino alcohol **80** was then obtained from **79**, and the amino acid **81** was prepared by oxidation and removal of the protecting group. Compound **81** is an isomer of 2,4-methanoproline, a natural non-proteinogenic α-amino acid with the carboxyl group at the ring junction, which showed interesting seed-protecting activity.[53]

Conclusions

This review illustrates some attractive aspects of the field of cyclobutene chemistry. A large variety of compounds can be prepared from cyclobutenes, including cyclopropanes and bicyclic products through electrophilic additions followed by ring contraction, involving rearrangement or intramolecular substitution as key steps. Cyclobutenes can also give rise to diverse dienes, which can act as useful precursors to several classes of compounds. Further application in the field of carbocyclic nucleosides are particularly stressed.

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