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Cycloartenol to *Buxus* alkaloids

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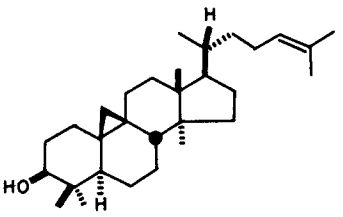
Abstract. Cycloartenol, a pentacyclic triterpene alcohol, has emerged as an obligatory intermediate in the biosynthesis of sterols in higher plants and algae. Cycloartenol has also been implicated in the biosynthesis of steroidal alkaloids. The *Buxus* alkaloids, which have a pregnane-type framework, are considered to arise from cycloartenol by catabolic processes with nitrogen incorporation at an appropriate stage, although no biosynthetic studies appear to have been carried out. Thus, cycloartenol is an important substrate in nature for elaborating a rather large group of secondary metabolites. In an effort to mimic some of these processes in the laboratory, we have carried out transformations of cycloartenol into *Buxus* alkaloids. New routes for side-chain degradation of cycloartenol and cyclolaudenol have been developed. A novel method for functionalization at C-16 has been worked out and a new strategy for regioselective oxygenation of 4-methyl has been exploited. Synthesis of buxandonine, cycloprotobuxine-F, cycloprotobuxine-A, cyclobuxophyllinine-M and 31-norcyclolaudenone have been achieved.

Keywords. Cycloartenol; *Buxus* alkaloids; cyclolaudenol; side-chain degradation; reductive alkylation; Buxandonine; cycloprotobuxine-F; cycloprotobuxine-A; cyclobuxophyllinine-M; Schenk oxidation; pyridinium chromate-on-silica gel; cycloeucalanone; 31-Norcyclolaudenone.

Cycloartenol (1), a pentacyclic triterpene alcohol, has emerged as an obligatory intermediate in the biosynthesis of sterols in higher plants and algae (see *e.g.* Goodwin 1979). Cycloartenol has also been implicated in the biosynthesis of steroidal alkaloids (see *e.g.* Heftmann 1983; Roddick 1980). The *Buxus* alkaloids, which have a pregnane type framework, are considered to arise from cycloartenol by catabolic processes with nitrogen incorporation at an appropriate stage, although no biosynthetic studies appear to have been carried out. Thus, cycloartenol is an important substrate for nature for elaborating a rather large group of (so-called) secondary metabolites. Chemists often seek to mimic nature's processes in the laboratory (see *e.g.* Scott 1976) and the work to be reviewed in this brief article summarises our efforts aimed at transformations of cycloartenol into *Buxus* alkaloids. Another reason for undertaking this research was the rather easy accessibility to cycloartenol and the related cyclolaudenol (2) from opium marc in which they occur in over 1% (separately) concentration (Narula and Sukh Dev 1971).

Before proceeding with the main theme it appears appropriate to preface this with a brief introduction to *Buxus* alkaloids. These compounds have a rather narrow distribution in nature and are restricted to the family Buxaceae consisting of six genera and some 80 species. Of these, the genus *Buxus* which is composed of over 10 species is responsible for almost all the known alkaloids of this type. So far, more than 70 alkaloids have been isolated and characterised. Of these, not less than 35 have been isolated from only one species—*Buxus sempervirens*. These plants occur in India only in the Himalayan region, that is from Kashmir, North Western Himalayas to North East. No work on these plants has been carried out in India and the entire work on *Buxus*



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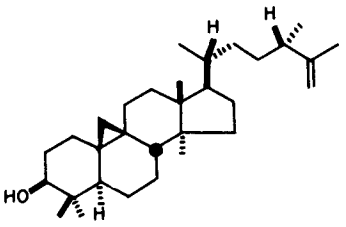
Cycloartenol



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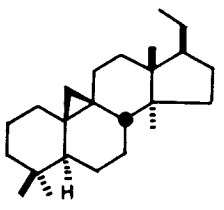
Cycloloudenol

alkaloids—isolation and structure determination—has been done abroad. These alkaloids are important because of their broad spectrum of pharmacological activity—against rheumatism, dermatitis, malaria, tuberculosis etc. They also have an important place in biochemical research (Tomko and Voticky 1973).

Chemical investigations were started as early as 1830. However, pure bases could be isolated only a century or so later and thus, all earlier work had been done on mixtures! There was intense structural activity between 1958 and 1962, in no less than nine laboratories. The first structure of the *Buxus* alkaloids—that of cyclobuxine-D—was elucidated in 1962 by Brown & Kupchan (1962). Two years later (Brown and Kupchan 1964), cyclobuxine-D was correlated with cycloeucalenol, a derivative of cycloartenol. As a result of these extensive studies, which were carried out in a number of laboratories, several structural varieties have been characterised. There are three main types (3, 4, 5) and all these are hexanor compounds based on cycloartenol: in structure 4, one more methyl is lost, while in 5, the six-membered ring has been expanded into a seven-membered ring by way of cleavage of the cyclopropane ring. Invariably, there is an amine function at C-3 or C-20; in a majority of cases both C-3 and C-20 carry this functionality. The C-20 functionality is always *S*-configurated, while at C-3, the nitrogen function is invariably β. Whenever, there is no nitrogen function at C-3 or C-20, there is an oxygen function instead, a carbonyl or an hydroxyl. Other usual positions for carbonyl/hydroxyl functions are: C-16, C-11 and C-4 methyls, especially the 4α-methyl. Olefinic linkage is usually found between C-2/C-3, C-6/C-7, C-16/C-17 or C-17/C-20.

With this background, we can now proceed to describe our work. When we started this work in 1970 there was only one report, that from Prof. Arigoni's laboratory (Calame and Arigoni 1964), on the conversion of cycloartenol into the *Buxus* alkaloid,



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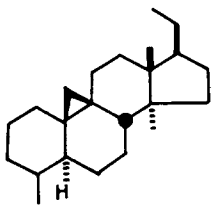

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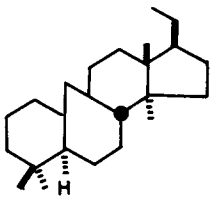

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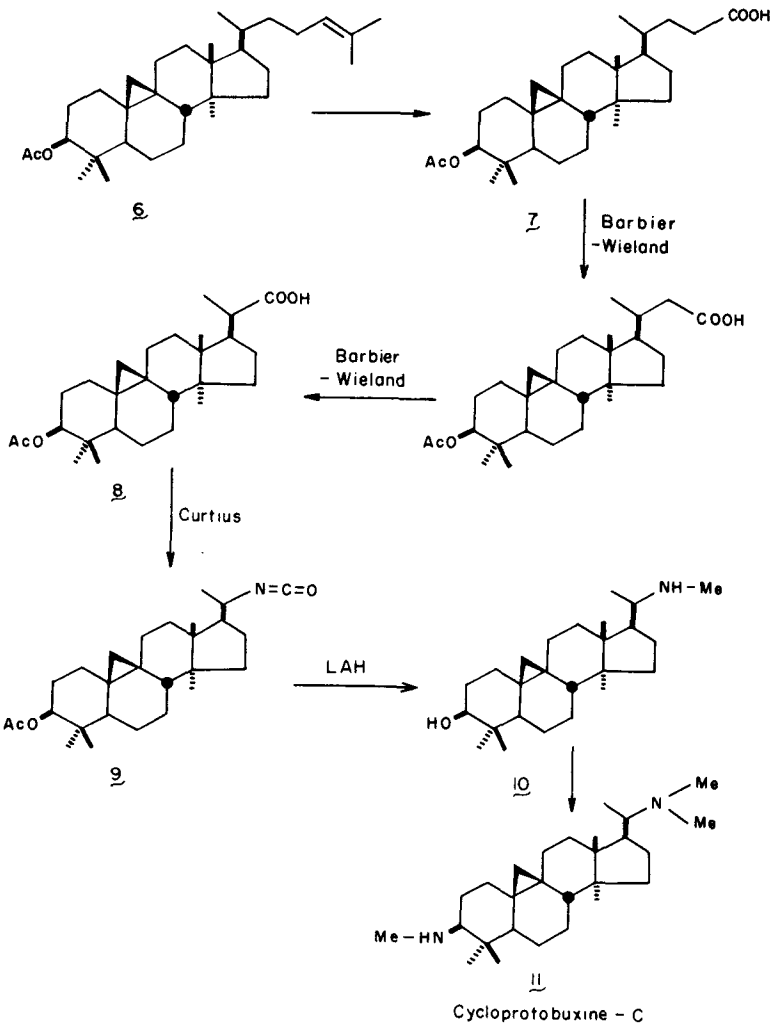
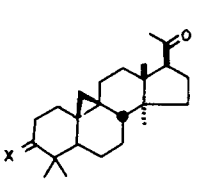


Figure 1. ETH route to cycloprotobuxine-C.

cycloprotobuxine-C. The route developed by these authors is shown in figure 1. Cycloartenyl acetate (6) was degraded by the usual method of ozonolysis to the corresponding acid (7), which by a double Barbier-Wieland degradation was converted to the pentanor acid 8. Curtius degradation led to the isocyanate 9, which on reduction gave the methylamine 10; the latter could be readily elaborated into cycloprotobuxine-C (11). We set before us the following scope:

(i) Side-chain degradation of cycloartenol to the hexanor derivative 12.
(ii) Development of a suitable method for C-16 oxygenation.
(iii) Regioselective oxygenation of 4α-methyl and elaborating it further to a nor-derivative.

Cycloprotobuxine-F (13), cyclobuxophyllinine-M (14) and cyclobuxosuffrine (15)



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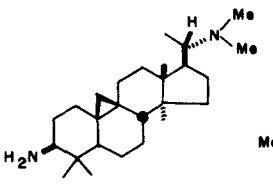
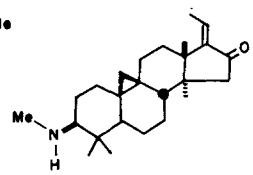


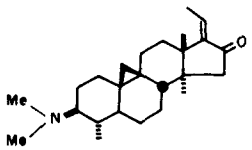
13 (17)

Cycloprotobuxine - F



14(38)

Cyclobuxophyllinine - M



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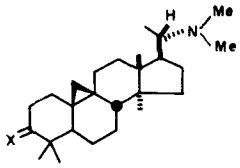
Cyclobuxosuffrine



Buxandonine (16) : X = O

Cycloprotobuxine - F (17/13) : X = H(α), NH_2

Cycloprotobuxine - A (18) : X = H(α), NMe_2

were selected as the representative target molecules, requiring one or more of the above transformations.

Buxandonine, cycloprotobuxine-F and cycloprotobuxine-A

The first phase of the work was directed towards synthesis of buxandonine (16) and the related alkaloids cycloprotobuxine-F (17) and cycloprotobuxine-A (18). Towards this end we developed efficient procedures for side-chain degradation, and these enabled us to convert cycloartenol (1) and the related cyclolaudenol (2) into the key hexanor derivative 12. Before we discuss these transformations, it will not be out of place to recount the state-of-art pertaining to side-chain degradation of triterpenes/steroids, in general, at the time we started our investigations. The classical Barbier-Wieland degradation (see *e.g.* Fieser and Fieser 1959) proceeds through Grignard reaction with phenyl magnesium bromide on an ester, followed by dehydration and oxidative cleavage of the resulting diphenylethylene giving the nor derivative (acid or ketone). The only other method available then was an important modification of this sequence first published in 1945, and known as the Meystre-Miescher modification (Meystre *et al* 1944, 1946). In this, an additional double bond is created through NBS bromination followed by dehydrobromination. Oxidative cleavage now results in reducing the chain by three carbons. This modification was investigated by Calame (1965) for side-chain degradation of cycloartenol, but the yields were extremely poor because the NBS reaction resulted in considerable opening of the cyclopropane ring. As matter of fact, only a year before this work we had demonstrated (Gaitonde *et al* 1964) that cyclopropane rings indeed open up on exposure to NBS.

Thus, our first objective became the development of new strategy for the side-chain degradation. Since the thermodynamic stability of an olefin increases with increasing alkyl substitution it should be possible to migrate an ethylenic linkage in a chain upto a point where the terminus is more substituted. Various reagents are available (see *e.g.*

Hubert and Reimlinger 1969, 1970) for such isomerizations: acids, bases or metals like palladium, nickel, rhodium etc. It was obvious that for the purpose on hand the most useful route would be base isomerization, as skeletal rearrangements and cyclopropane ring cleavage must be avoided. A variety of bases have been used including potassium *tert*-butoxide in *tert*-butanol, potassium *tert*-butoxide in dimethyl sulphoxide, high surface sodium, lithioethylene diamine, etc. Thus, for the immediate purpose, it was planned to suitably modify cycloartenol molecule to get a nor-olefin with a terminal olefinic bond suitable for isomerization towards the ring. The sequence finally worked out (Narula and Sukh Dev 1971) is shown in figure 2. The first step was to cleave the side-chain at the olefinic linkage to get the carboxylic acid (20). Surprisingly, ozonolysis of cycloartenyl acetate (19) has been reported (Bentley *et al* 1953) to give none of this acid. To overcome this difficulty we finally succeeded in devising a modified procedure

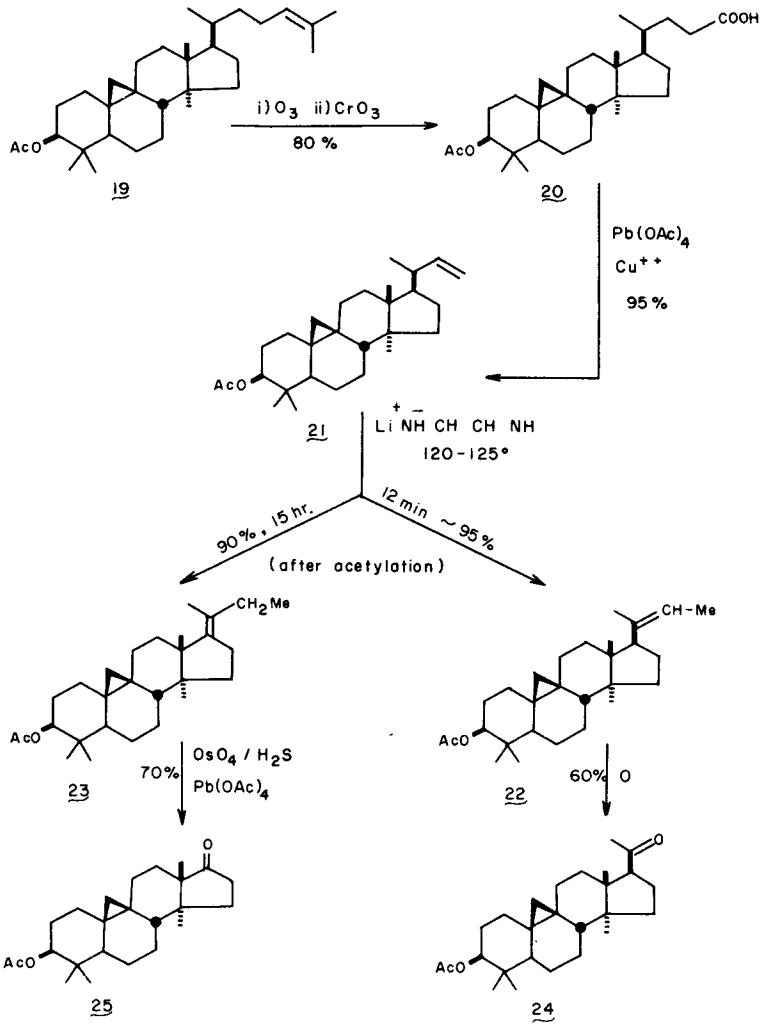


Figure 2. Side-chain degradation of cycloartenol.

(Narula and Sukh Dev 1969) entailing chromic acid oxidation of the ozonide, which gave the trisnor acid in excellent, consistent yields. This sequence has been applied to several other olefins and the results have always been superior to those reported earlier. Oxidative decarboxylation with lead tetraacetate in the presence of Cu^{++}, according to Kochi and coworkers (Bacha and Kochi 1968; Kochi *et al* 1969), furnished an excellent yield of the tetranorolefin (21). This could now be isomerized by a suitable base. Our choice fell on lithioethylenediamine (Reggel *et al* 1958; Tyagi *et al* 1962) which is a rather strong base. Depending on the time of exposure to the reagent, we could get the trisubstituted (22) or the tetrasubstituted olefin (23). Ozonolysis of 22 furnished the required hexanorketone (24). The tetrasubstituted olefin was also oxidatively cleaved, as shown in figure 2 to the octanor-cyclopentanone (25) which was needed for certain other conversions in the steroid area (Narula and Sukh Dev 1971). Later, based on this concept of base-catalysed isomerization of olefins, a very simple route to the target molecules 24 and 25 could be developed (Narula and Sukh Dev 1971; Singh *et al* 1977): cycloartenol itself was subjected to base-isomerization, the product acetylated and the ozonide oxidised by Jones' reagent to get about 25% acids (not investigated further), and a neutral fraction from which 24 and 25 could be isolated in yields of 30% and 15% respectively, based on cycloartenol. Evidently, in terms of the time involved and the cost, this method came very handy and was used for the preparation of the required intermediate (24).

Cyclolaudenol (2) could also be degraded (Narula and Sukh Dev 1971) to the same required hexanorketone 24 by a slight modification of this sequence: the main idea was to get to the trisnoracid (20) from cyclolaudenol, and then proceed to the target molecule, as already discussed. Cyclolaudenol was isomerised to the thermodynamically more stable double bond isomer, which after acetylation was subjected, sequentially, to ozonolysis and hypobromite oxidation and acetylation to furnish the same trisnoracid (20). Another alternative method (Singh *et al* 1977) for the degradation of cyclolaudenol for the same purpose was also worked out and is summarised in figure 3. Ozonolysis of cyclolaudenyl acetate, followed by $NaBH_4$ reduction yielded the nor-alcohol (26), which on exposure to hypoiodite, fragmented to the iodide (27; X = I). The corresponding chloride (27; X = Cl) was readily reached by the sequence shown (figure 3): isomerization followed by ozonolysis to get ketone 28, reduction to the alcohol 29, followed by reaction with $POCl_3$ to give the chloride 27. Both of these halides, iodide or the chloride, could be converted by treatment with lithio ethylenediamine into olefin (30), suitable for degradation by ozone to the required hexanor ketone (24). It may be noted that lithio ethylene-diamine caused dehydrohalogenation and isomerization of the resulting olefin in one experimental step.

Thus, we could develop several methods for the preparation of the key intermediate 24, required for further elaboration into *Buxus* alkaloids. At this stage, it may be pointed out that while we were engaged on these investigations two publications describing preparation of the hexanorketone (24) appeared. Adam *et al* (1970) described a 15-step degradation of cycloartenol to 24, a series of Hofmann acidamide degradations being employed. Another group (Nakano *et al* 1970) reported its elaboration from lanosterol (31), through the intermediate 32, already described by Ruzicka many years earlier (Voser *et al* 1952).

It is gratifying to note that the side-chain degradation sequence, as developed by us, has been exploited by other workers, later, for side-chain degradation of lanosterol (Kreiser and Ulrich 1976).

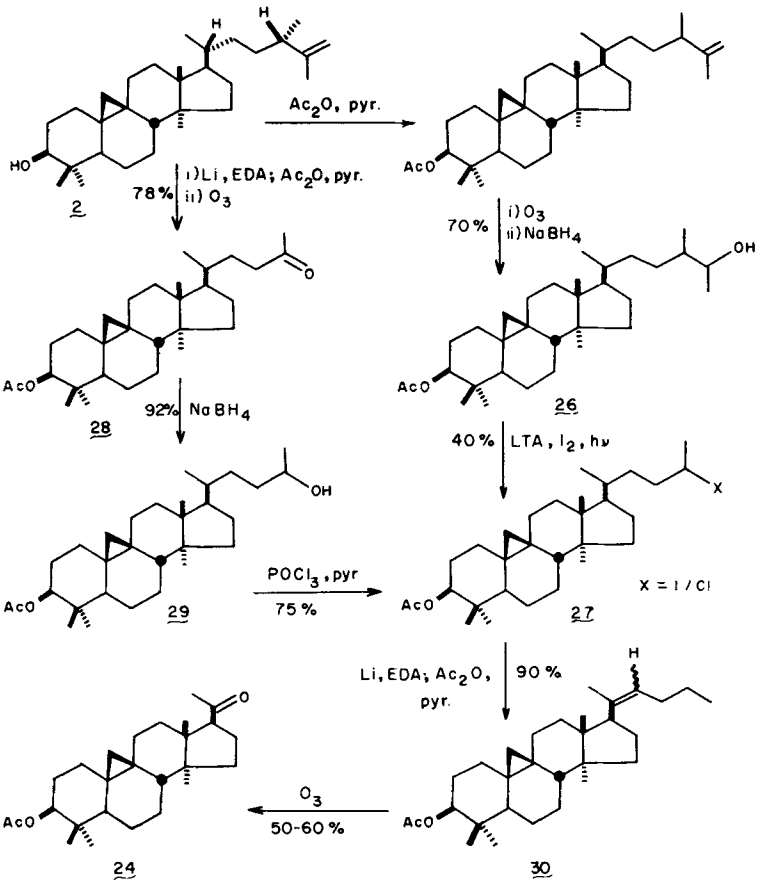
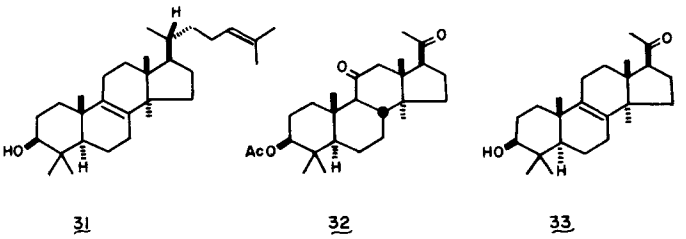
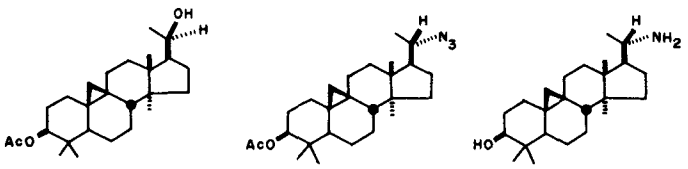


Figure 3. Side-chain degradation of cyclolaudenol.



After having developed viable methods for the conversion of cycloartenol or cyclolaudenol into the hexanorketone 24, stage was set for its elaboration into simple *Buxus* alkaloids of type 3. Towards this end, one must convert C-20 carbonyl into an amino function with the required *S*-chirality, and C-3 oxygen function into a β-amino derivative. The latter conversion is straightforward, as hydrogenation or reduction of carbon nitrogen or carbon oxygen or carbon carbon double bond in the steroid nucleus takes place, preponderatingly, from the α-face to furnish stereoselectively the β-product. However, conversion of C-20 carbonyl into an amine function with the

required configuration is less simple. Since, the reduction of 20-oxo-pregnanes with complex hydrides is known (Kirk and Hartshorn 1968a) to furnish predominantly *R*-configurated alcohols and since, the immediate environment at C-20 in 24 is similar to that in 20-oxo-pregnanes, it was argued that a similar hydride reduction of 24 would furnish as the chief product a 20*R*-alcohol. Furthermore, since the reduction of oximes or imines is mechanistically akin (Kirk and Hartshorn 1968b) to the reduction of ketones, routes to the C-20 amine using such intermediates, would result predominantly in the unwanted *R*-chirality. Hence, the most promising approach appeared to be one involving a single $S_N i$ displacement of a suitable C-20 derivative. The sequence successfully worked out (Singh and Sukh Dev 1977) involved reduction of the hexanorketone acetate (24) by $NaBH_4$ to give the R-alcohol (34) as the major product, which *via* tosylation and displacement by sodium azide could be converted into the azide 35. This latter reaction proved quite unsatisfactory and it was after a lot of experimentation that satisfactory conditions could be established and these required hexamethylphosphoric triamide as a solvent and ~ 25° as the reaction temperature. Yields of ~ 65% could thus be secured. This compound was then reduced by LAH to the corresponding amine (36), which now has the right stereochemistry.



34 35 36

With these methods on hand it was rather simple to convert 36 into the targeted *Buxus* alkaloids. This is shown in figure 4 (Singh and Sukh Dev 1977). It may be noted that the key amine (36) is available in eight steps from cycloartenol. Reductive alkylation (Leuckart reaction) of 36 gave the dimethyl derivative 37, which on Jones' oxidation furnished buxandonine (16), a minor alkaloid of *Buxus sempervirens* (Dopke and Muller 1967). Transformation of its carbonyl function *via* oximation and LAH reduction to amine results in cycloprotobuxine-F (17), which, by reductive alkylation was converted into cycloprotobuxine-A (18). These alkaloids occur in *Buxus madagascarica* and *Buxus balearica* respectively (Tomko and Voticky 1973).

Cyclobuxophyllinine-M

In the next phase, attention was directed to the conversion of cycloartenol *via* the hexanorketone into C-16 oxygenated *Buxus* alkaloids. Specifically, our aim was to synthesise cyclobuxophyllinine-M (Buxenone-M) (38), an alkaloid isolated from *Buxus microphylla* var. *Suffruticosa* and *B. sempervirens* (Nakano *et al* 1966; Dopke *et al* 1966). This compound has been earlier converted into the related *Buxus* alkaloids cyclobuxophylline-K (39) and buxanine-M (40) (Nakano *et al* 1966; Dopke and Muller 1966).

Elaboration of the hexanorketone (24) to the targeted cyclobuxophyllinine-M (38) would involve: (i) generation of *E*-configurated $\Delta^{17(20)}$-16-keto system, and

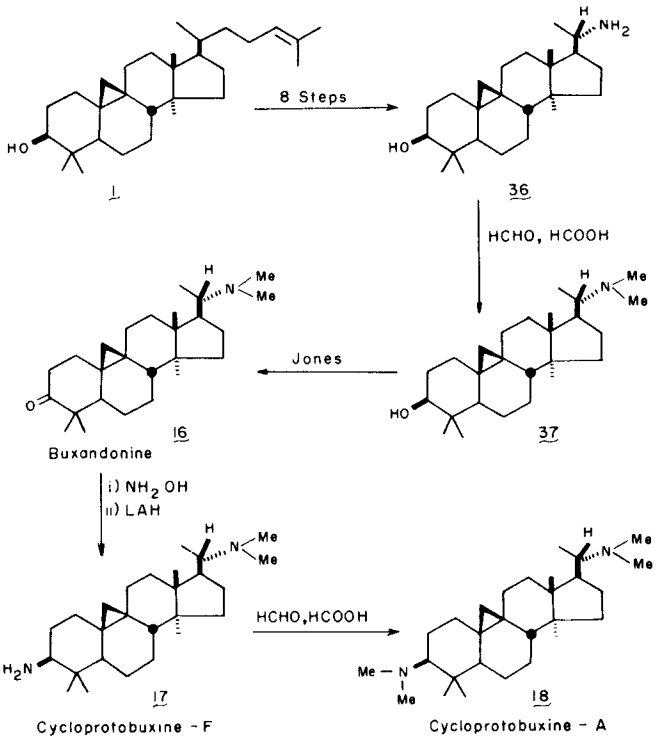
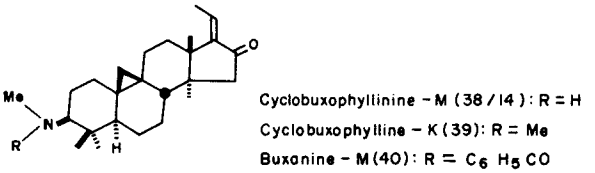
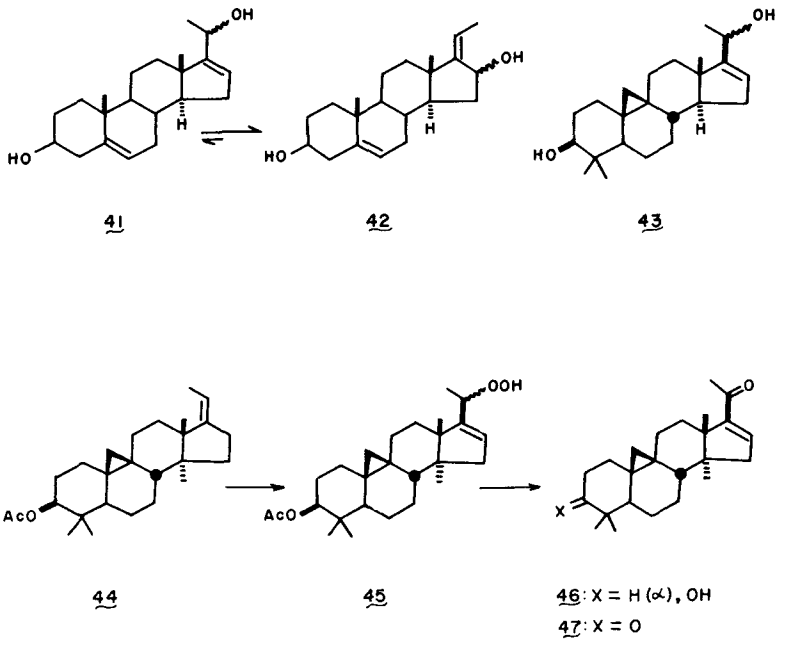


Figure 4. Synthesis of buxandonine, cycloprotobuxine-F and cycloprotobuxine-A.



(ii) conversion of 3β-acetoxy group into 3β-methylamino function. For the introduction of the $\Delta^{17(20)}$-16-keto function, advantage was sought to be taken of the known (Benn and Dodson 1964) acid-catalysed isomerization of pregn-16-en-20-ols to preg-17(20)-en-16-ols, while the introduction of the 3β-methylamino group appeared reasonably feasible by the standard (Emerson 1948; Borch *et al* 1971) reductive amination of the 3-keto function. However, sequence of reactions had to be so chosen that the oxygenated functions at C-3 and C-16/C-20 are properly differentiated.

It has been well-established (Benn and Dodson 1964) that acid-catalysed equilibration of steroidal allylic alcohols of type 41 generates an isomeric mixture in which the isomer 42 predominates. It has also been established that configuration at C-20 has no effect on the equilibrium. Also, the olefin which is formed is always *Z*-configurated and the stereochemistry at C-16 is preponderatingly β. Since in a cycloartane analogue such as 43, the D-ring structure is essentially similar to that in the steroid case, just discussed,



it should be possible to isomerise such an alcohol to the more stable 17(20)-ene-16-ol. Thus the immediate requirement became the synthesis of such a compound from the hexanorketone. This was achieved in two ways (Desai *et al* 1981). In one approach the hexanorketone was converted into olefin 44 *via* reduction, tosylation and dehydrotosylation with collidine in ~ 70% yield. This on Schenk oxidation, in the presence of methylene blue, gave the required hydroperoxide 45, which on treatment with acetic anhydride furnished the required unsaturated ketone 46. The same olefinic ketone could be more directly prepared by bromination of 24 followed by dehydrobromination. Hydrolysis, followed by chromic acid oxidation yielded the diketone 47, which had been obtained earlier by Ruchig degradation of the *Buxus* alkaloid cyclovirobuxine-D (Brown and Kupchan 1964).

The series of reactions, which permitted the successful transformation of the unsaturated ketone 46 into cyclobuxophyllinine-M (38) is shown in figure 5 (Desai *et al* 1981). LAH reduction of 46 gave the diol 43 in which the two hydroxyls should now be distinguished. It was found that one could conveniently acetylate the allylic hydroxyl function by acetic acid in the presence of a trace of toluene sulphonic acid and we thus obtained acetate 47 in about 80% yield. This was next oxidised by chromic acid to 48; for this we utilized pyridinium chromate-on-silica gel—a convenient off-the-shelf Sarett-type reagent, introduced by us sometime back (Singh *et al* 1979). This, on isomerization in the presence of acetic acid, acetic anhydride and toluene sulfonic acid, furnished as the major product 49 with *Z*-configuration. This was then converted into the methylamino derivative by reductive amination, using methylamine, sodium cyanoborohydride in MeOH in the presence of type A_4 molecular sieves. The product 50 was saponified and the resulting hydroxy compound oxidised by active MnO_2 to furnish 51, which differs from the target compound in being its *Z*-geometrical isomer.

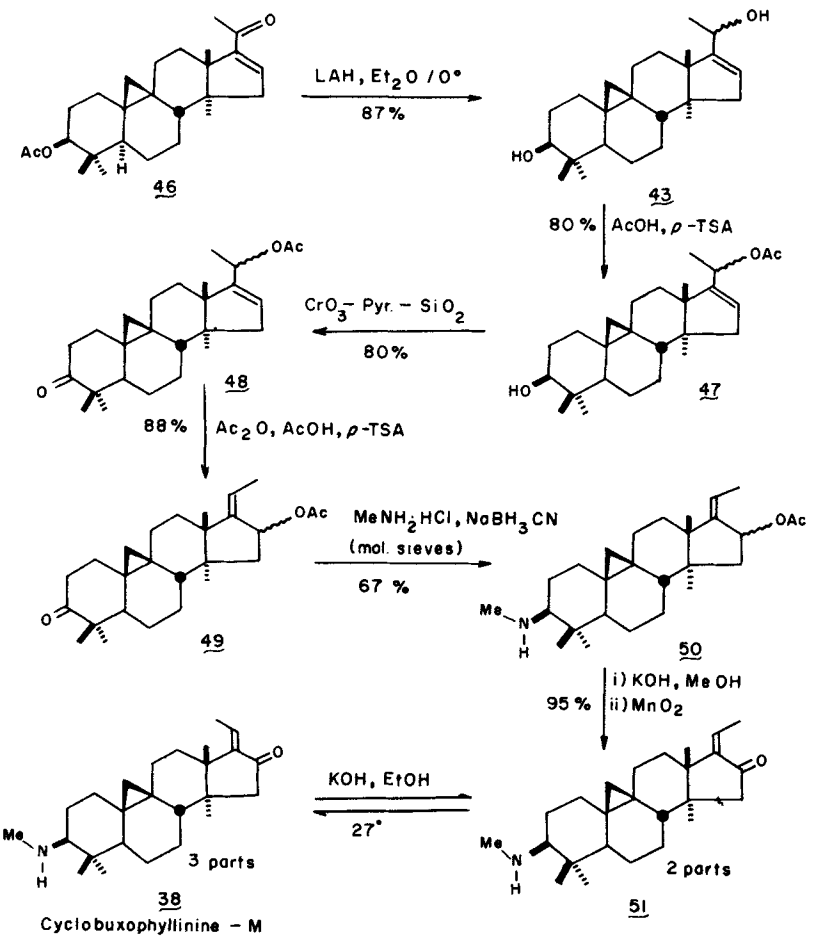
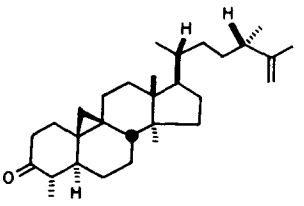


Figure 5. Synthesis of cyclobuxophyllinine-M.

On equilibration with ethanolic KOH, a 3 : 2 ratio of the *E* and *Z* isomers resulted, from which the required cyclobuxophyllinine-M (38) could be isolated by fractional crystallisation.

Cycloeucalanone and 31-*norcyclolaudenone*

The third phase of our investigations was aimed at development of a method for the regiospecific/regioselective functionalization of C-4α-methyl. Such a method was necessary for the synthesis of *Buxus* alkaloids lacking a C-4 methyl or oxygenated at one of these (invariably the α-methyl). An example of such an alkaloid is cyclobuxosufferine (15). As an immediate objective, we set before us the conversion of cyclolaudenol into 31-norcyclolaudenone (52) a component of *Musa sapientum*. It may be pertinent to point out at this stage that at the time we started this work several methods were available for desmethylation of C-4, especially because there has been a lot of interest in mimicking this transformation, which is an obligatory step in the conversion of



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triterpenes (lanosterol) into steroids. In the biological system, specific 4-α-methyl hydroxylation occurs (Rees and Goodwin 1972; Nelson *et al* 1975a). Two approaches have been described. In the first approach, ring A′ is cleaved to get a 3,4-seco derivative, which is further manipulated towards the desired end (see *e.g.* Cohen *et al* 1973). In the second approach direct functionalization of a C-4 methyl is aimed at. In a method, reported in 1975 (Nelson *et al* 1975b), an N-oxyl derivative is prepared and photolysed resulting in oxygenation of the axial methyl (*i.e.* 4β-methyl). A second method utilises thermal cleavage of an azidoformate, leading to functionalization of the 4α-methyl as well as of C-2, almost to the same extent (Jones *et al* 1976). Another method, reported in 1977 (Midgley *et al* 1977), is not very versatile as it requires a C-6/C-7 double bond: through hydroboration, C-6 alcohol is obtained, the nitrite of which is photolysed to effect selective 4α-functionalization.

As can be seen, all the above methods are either rather involved or have poor regioselectivity. For our purpose on hand, we thought it worthwhile to develop a more selective method. Figure 6 depicts our approach to the problem. The well-known photolysis of suitably constituted hypoiodites, leading to an ether/iodoether, readily convertible into the corresponding lactone, appeared appropriate. The structural and stereochemical requirements of this reaction have been well-delineated (see *e.g.* Heusler and Kalvoda 1964, 1972). The reaction proceeds well in the desired direction only if the internuclear distance between the oxygen and the concerned carbon falls between 2·5 and 2·7 Å, and a 6-membered chair conformation transition state is possible. In terms of these considerations, a β-hydroxymethyl function at C-3 on a triterpene nucleus (e.g. 53) appeared suitable for functionalization of C-4 methyls, as the distance between O and either of the C-4 methyl C falls in the desired limit and a 6-membered chair conformation transition state is also feasible (54, 55). However, a closer scrutiny reveals that functionalization of 4α-methyl should be preferred for the following two reasons: (a) in conformation 54, the 6-membered transition state simulates a *trans*-fused relationship with ring A and hence should experience less 1,3-diaxial type interactions and should be preferred over 55 which has a similar '*cis*-fused' disposition, (b) in 54 C-OH is flanked by a 'small' (H atom) and a 'large' (C-4) groups in contrast to 55 in which these groups are 'medium' (C-2) and 'large' (C-4). Thus, if these reasonings are correct, one can expect a high degree of regioselectivity for the reaction, resulting in the desired functionalization of 4α-methyl.

To evaluate this strategy conversion of cyclolaudanone (56) to the known cycloeucalanone (64), along the lines shown in figure 7, was investigated (Desai *et al* 1982a). Cyclolaudenone was converted *via* Wittig reaction into the methylene derivative 57 which was hydroborated to give a mixture of the β (major) and α methanols; the major product was recognised as β from its spectral data. It was

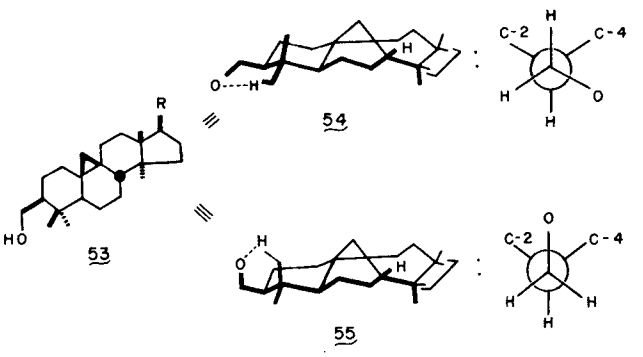

Figure 6. Preferred conformations in the functionalization reaction.

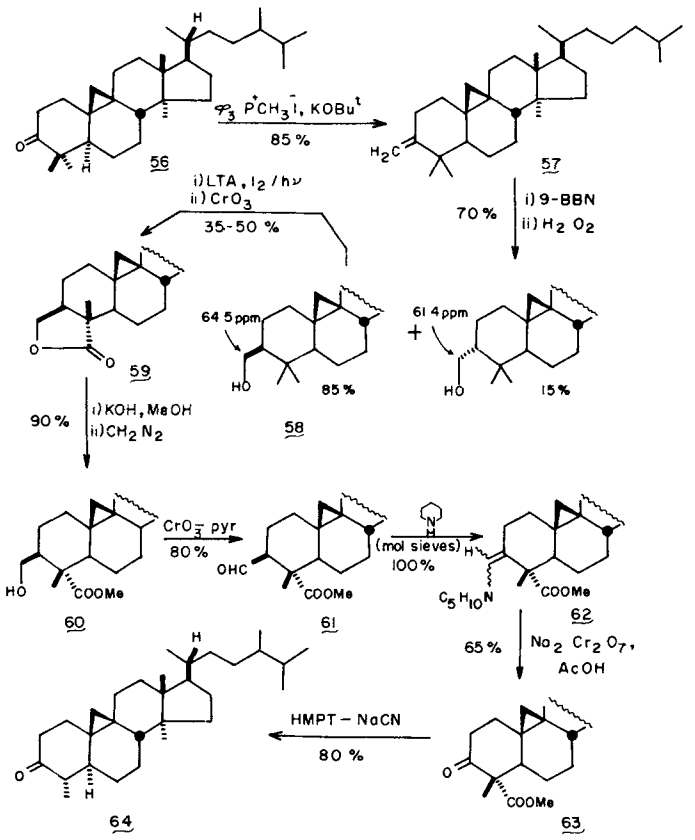

Figure 7. Synthesis of cycloeucalanone.

subjected to the action of LTA/I_2/*hv*, and the crude product from the photolysis reaction oxidized with chromic acid to give lactone 59 in yields of 35–50%. The lactone on base hydrolysis, followed by esterification with diazomethane furnished 60. The methoxycarbonyl group in 60 was readily assigned α-configuration on the basis of its

spectral characteristics, especially its ^{13}C-NMR spectrum. Oxidation of 60 with CrO_3-pyridine smoothly furnished the corresponding formyl ester (61). This was converted into the corresponding enamines (*E*/*Z*), which were directly oxidised ($Na_2Cr_2O_7$-AcOH) to furnish the desired β-keto ester (63) in an overall yield of 50% from the hydroxy ester 60. Exposure of 63 to NaCN in hexamethylphosphoric triamide resulted in hydrolysis with concomitant decarboxylation to furnish the known cycloeucalanone (64) in over 80% yield.

The successful completion of the above transformation vindicated the strategy we had envisaged for regioselective functionalization of 4α-methyl in a triterpene system. We were now all set to apply this method to a more difficult case, namely, the conversion of cyclolaudenol into 31-norcyclolaudenone (52), a triterpene isolated from *Musa sapientum* (Knapp and Nicholas 1970). Figure 8 summarises the sequence of reactions successfully exploited for the purpose (Desai *et al* 1982b). It was clear from the outset that the olefinic bond in the side-chain of cyclolaudenol (2) would have to be protected in a manner that the sequence of reactions for the functionalization of 4α-methyl and final removal of C-29 can be easily carried out and after these operations,

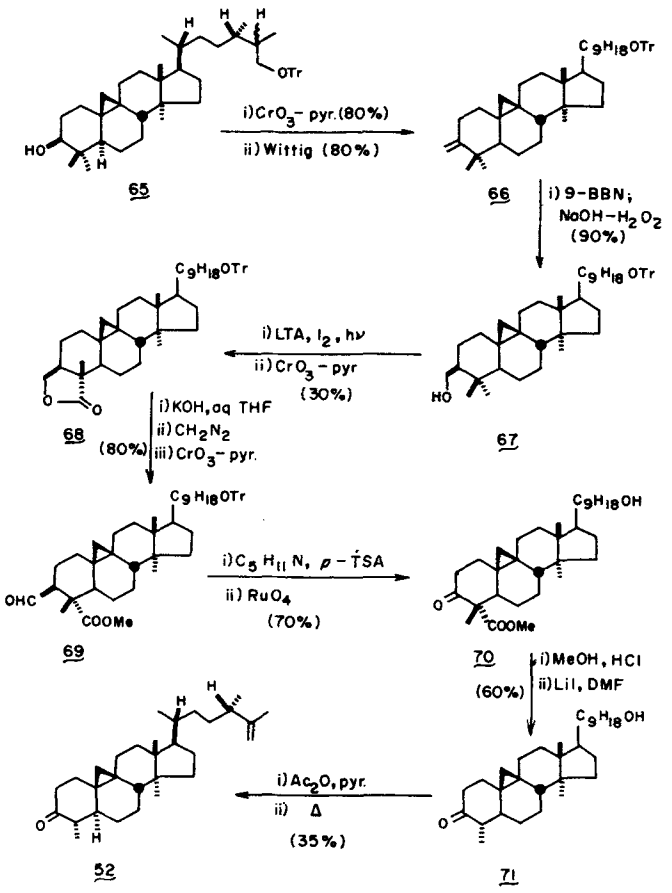

Figure 8. Transformation of cyclolaudenol to 31-norcyclolaudenone.

the double bond can be regenerated. On hydroboration followed by oxidative work-up, cyclolaudenol furnished a mixture of epimeric 26-hydroxycyclolaudan-3β-ols, in which the primary hydroxyl could be smoothly protected by tritylation. The trityl derivative 65 was oxidised with CrO_3-pyridine to the corresponding ketone, which was converted to the methylene derivative 66, as before. This on hydroboration (with 9-BBN)-oxidation gave a product, of which the major component (diastereomeric at C-26) was assigned 3β-configuration (67) based on the expected preferential attack by the hydroborating agent from the less hindered α-face of the olefins (66). Irradiation of alcohols 67 along with the 3α-isomers, in the presence of LTA and iodine, followed by Collin's oxidation, gave a product from which lactones 68 were isolated by inverted-dry-column chromatography (Bhalla *et al* 1967). Spectral data were fully consistent with the assigned structure. Lactones 68 were hydrolysed and esterified to give hydroxyesters, which on oxidation with Collin's reagent gave the formyl esters (69). The latter were converted to their enamines, and conveniently cleaved with RuO_4 to the keto esters 70. Incidentally, this is the first report of the use of RuO_4 for the cleavage of C=C bond in enamines. Exposure of 70 to methanolic HCl resulted in detritylation to the alcohols which were subjected to saponification-decarboxylation, in presence of LiI/DMF to get the nor-derivative 71. This material was acetylated and pyrolysed to furnish the required 31-norcyclolaudenone (52). The product was characterised by the usual spectral methods and the data were identical to those reported for the natural product.

We hope to extend the above methodology to the conversion of cycloartenol/cyclolaudenol into cyclobuxosuffrine (15), a typical *Buxus* alkaloid lacking a C-4 methyl.

Acknowledgement

The work described in this paper has been possible with the dedicated efforts of my students and colleagues, whose names appear in the various references. The author takes this opportunity to express his sincere thanks and appreciation. Special mention must be made of the contributions of Dr H P S Chawla who was actively involved in the third phase of this work. It is a pleasure to specially thank him for his collaboration.

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