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# Synthesis of natural products using chiral glycol precursors

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Abstract The potentiality of the "chiral glycerol units" in the synthesis of a wide variety of optically active natural products is presented. Versatile applicability of the "glycerol units" is illustrated in two different manners: (1) by stereoselective reaction of glycerol-derived γ-lactone intermediates which leads to selective construction of tertiary and quaternary chiral centers and (2) by the intramolecular hetero-Diels-Alder reaction of glycerol-derived substrates which leads to a one-step construction of three consecutive chiral centers.

## INTRODUCTION

Synthesis of optically active natural products using naturally occurring optically active materials is the most efficient way when their availability and adaptability are fulfilled. However, such cases are rare as a great variety of natural products exist while adaptable chiral compounds are very limited. Therefore, finding certain common chiral pools adaptable to versatile target molecules is one of the most important tasks in organic synthesis.[1] In this lecture, I wish to present our results concerning the utility of "glycerol units" as common chiral pools employing two types of key reactions making the glycerol units adaptable to the construction of a wide variety of natural products. The major reasons for using "the glycerol units" are:

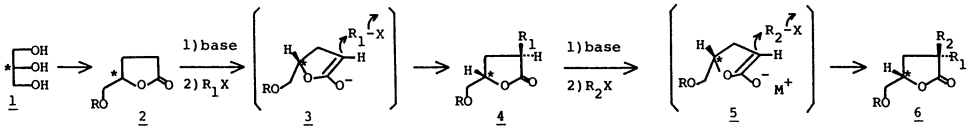
1) highly functional-----although "glycerol units" are the smallest chiral units, they possess sufficient functionalities.
2) latently symmetrical-----they can be used as both enantiomers either by inversion of chirality or chemoselection at both ends.
3) readily available-----available from naturally abundant sugars.
4) asymmetrically obtainable-----although not practical at the present, "glycerol units" can be prepared by asymmetric synthesis, such as the Sharpless epoxidation reaction.

This lecture will be concentrated on two main subjects depending on the types of the key reactions regarding: 1) syntheses via γ-lactone intermediates; 2) syntheses via intramolecular hetero-Diels-Alder reaction.

## 1. SYNTHESIS VIA THE γ-LACTONE INTERMEDIATES

Scheme 1 exhibits a basic concept for utilization of the "glycerol units" via the γ-lactone intermediates. In these conversions, a new chiral center is constructed at the α-position of the γ-lactone intermediates (2) and (4)

***Scheme 1***



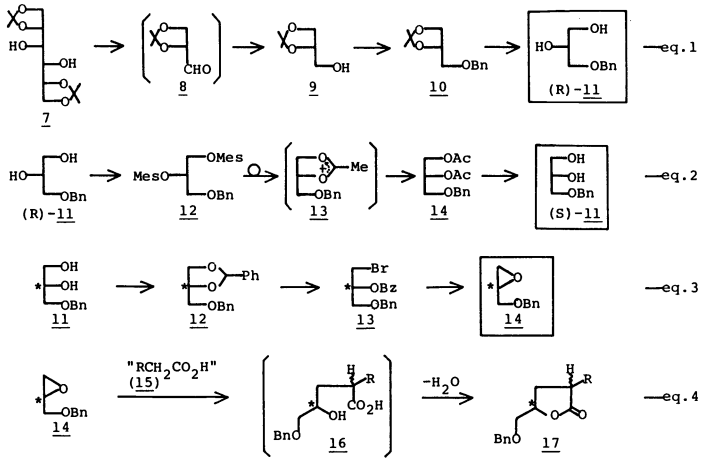

stereoselectively by a blocking effect of the substituent on the γ-carbon atom the chirality of which originates from the "glycerol units". An essential point is the preferred introduction of an electrophile from the less hindered face of the enolates (3) and (5) derived from the lactones (2) and (4) in the presence of a strong base. Accordingly, both tertiary and quaternary centers with requisite chirality may be constructed at the α-position of the lactone intermediates regardless of the chirality at the γ-position since the initial-

ly formed tertiary center may be inverted by protonation after enolate formation while the enantiomeric quaternary center can be constructed by sequential alkylation in reversed order.

### Synthesis of 'glycerol units' and their conversion into γ-lactone intermediates

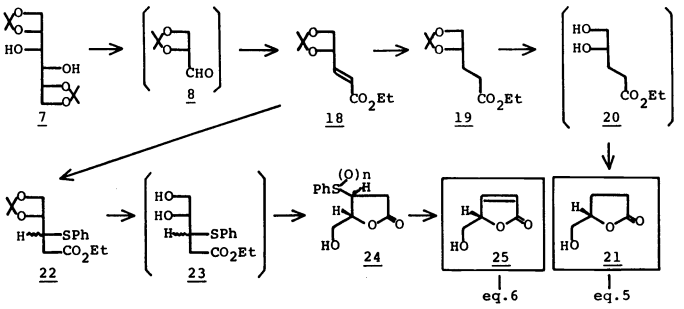
Although various methods have been reported for the preparation of the "glycerol units",[2] we chose D-mannitol diacetonide as a common starting material whose conversion into the γ-lactone intermediates is summarized in Schemes 2[3-5] and 3.
In these conversions the γ-lactone intermediates could be prepared in large quantities without isolation of glyceraldehyde acetonide (8) whose instability has so far prevented a large scale preparation. Thus, the glyceraldehyde (8) generated from the diacetonide (7) in water by periodate cleavage was reduced in the same solution with sodium borohydride to give glycerol acetonide (9) which was sequentially benzylated and acid hydrolyzed to give glycerol benzyl ether (11) (eq. 1).[3] Inversion of the chirality could be efficiently accomplished in good overall yield in complete inversion by treating the dimesylate (12) with potassium acetate in hot acetic anhydride followed by methanolysis (eq. 2).[4] Conversion of both enantiomeric glycerol units into the γ-lactone (17) was carried out using glycidol benzyl ether (14) whose

***Scheme 2***




efficient preparation could also be established by treating the benzylidene acetal (12) prepared from (11) with N-bromosuccinimide followed by sodium hydroxide (eq. 3).[5] The epoxide (14) was then condensed with a suitably substituted acetate unit (15) to give α-substituted γ-lactone (17) as a syn- and anti-mixture (eq. 4)[3]. This could easily be converted stereoselectively into either the syn-epimer by protonation or the quaternary substituted lactone by alkylation. This procedure is especially suited for the introduction of a vinylic or arylic substituent which cannot be introduced directly as an electrophile. On the other hand, the aldehyde (8) generated in water was condensed in situ with phosphonoacetate in the same aqueous solution in the presence of potassium carbonate to give the α,β-unsaturated ester (18) which on sequential hydrogenation and acid hydrolysis afforded the γ-lactone intermediate (21) in good overall yield (eq. 5).[6] Inversion of the chirality of this lactone was readily accomplished by us and other workers.[7] This γ-lactone (21) has also been prepared from glutamic acid,[7] however, it requires much tedious manipulations. Although we have not yet utilized it,

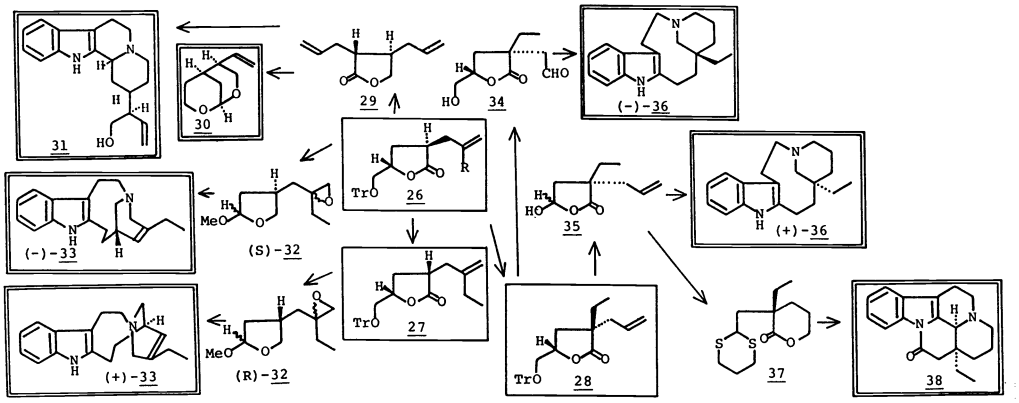
***Scheme 3***



another potentially useful chiral unsaturated γ-lactone (25) could also be prepared from the same unsaturated ester (18) via the sulfide (24) as shown (eq. 6).[6] Selectivity in the alkylation and the protonation was not always high enough especially when the benzyloxy-γ-lactones were being used, however, in most cases separation of the epimers could be easily carried out by recrystallization or by column chromatography.

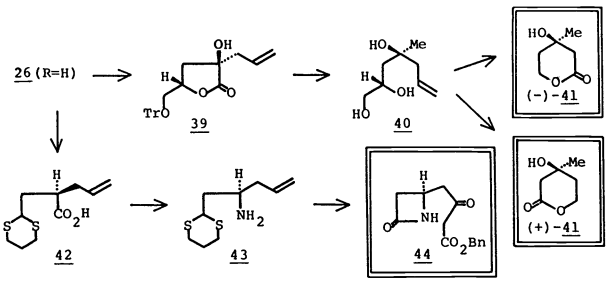
Utilization of the alkylated lactones may be exemplified in the enantioselective synthesis of a secoiridoid monoterpene and typical secoiridoid derived indole alkaloids: (i) The allyl lactone (26 : R=H) could be converted into the secoiridoid monoterpene (-)-semburin (30)[9] and the corynanthe type indole alkaloid (-)-antirhine (31)[10] via the diallyl lactone (29). (ii) Both epimers of the 2-ethylallyllactone, (26 : R=H) and (27), could be converted into the iboga alkaloids, both naturally occurring, (+)- and (-)-cleavamines (33),[11,12] respectively. (iii) The dialkylated lactone (28) could be converted into both the naturally occurring aspidosperma alkaloids (+)- and (-)-quebrachamine (36)[13,14] selectively based on its latent symmetric structure. (iv) The same lactone (28) could also be converted into the eburnane alkaloid of medicinally important (-)-eburnamonine (38)[15,16] (Scheme 4). The allyllactone (26 : R=H) could also be utilized as the starting

***Scheme 4***



material for both epimers of mevalonolactone (41)[17], the (+)-epimer of which being naturally occurring and known to be the biogenetic precursor of the iridoids and the indole alkaloids, via stereoselective oxidation. Furthermore, the same lactone (26 : R=H) served as a precursor for the starting material for the key intermediate (44) of the β-lactam antibiotics[18] (Scheme 5).

***Scheme 5***



Utilization of the epimeric γ-lactone mixtures (17) obtained from glycidol benzyl ether (14) is illustrated in the first enantioselective synthesis of nuciferol (46),[19] mesembrine (48),[20] physostigmine (50),[21] and marine sterol[56] (26) and an alternative synthesis of desmosterol[22] (53) as shown in Scheme 6. As appeared in Scheme 6, the protonation was not always directed by the chirality at the γ-position but by those of the α-substituent (eq. 8). It was also found that the selectivity is influenced by the nature of the α-substituent and the chirality of the proton source. While both achiral and chiral proton sources exhibited no significant difference in selectivity compared to the lactone substrate carrying simple α-alkyl groups, the substrates carrying vinyl, allyl, and aryl groups at the α-position were greatly influenced by the chirality of the proton sources as shown in Table 1.[25]. In particular, the α-vinylic lactone (57) obtained from the α,β-unsaturated carboxylic acid in a mixture of epimers furnished the syn epimer (58) in complete stereoselection from which four types of the irregular monoterpenes, lavandulol (59), cis-chrysanthemol (60), rothrockene (61), and santolinatriene (62) were obtained in chiral forms (Scheme 7). The observed chirality dependence in the proton-

***Scheme 6***

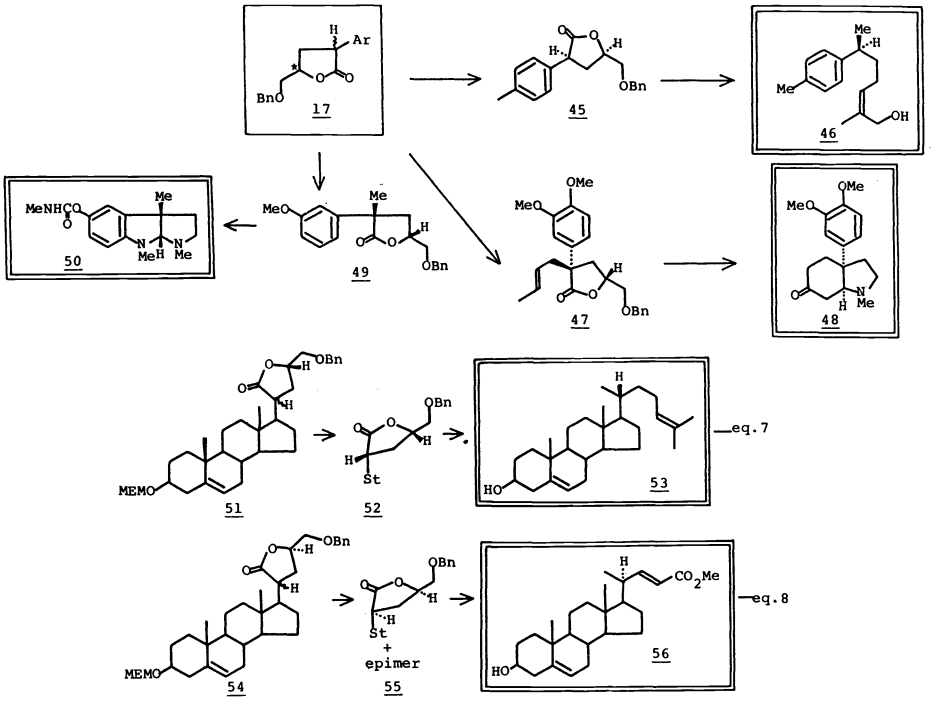
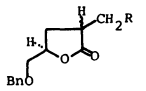
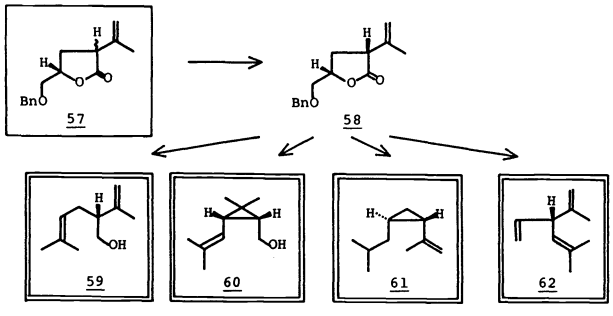



*Table 1*



| | aq.HCl or aq.$Na_2SO_4$ | (d)-CSA | (l)-CSA | 1)TMSCl 2)$CF_3CO_2H$ |
|---|---|---|---|---|
| 63 (R=H) | 2.9 : 1 | 2.45:1 | 2.73:1 | 3.6 : 1 |
| 64 (R=-$CH_2CH_2CH$=$C(Me)_2$) | 2.9 : 1 | 2.72:1 | 2.58:1 | 5.4 : 1 |
| 57 (R=-$C(Me)=CH_2$) | 1 : 0 | - | - | - |
| 65 (R=-Ph) | 4.5 : 1 | 2.46:1 | 5.87:1 | 1.1 : 1 |
| 26 (R=H) | 4.03:1 | 3.4:1 | 8.36:1 | 5.56: 1 |
| 26 (R=Et) | 10.2:1 | 9.22:1 | 2.47:1 | 4.9 : 1 |

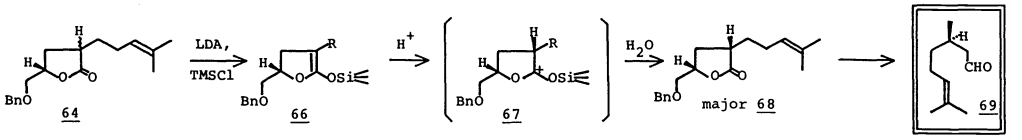
***Scheme 7***




ation strongly suggests that a matched proton source should be selected when a chiral proton source is used. Since we reasoned the observed low selectivity to be attributable to preferential O-protonation over C-protonation which sequentially isomerized to the lactone in less stereoselective fashion, the lactone (64) was first converted into the trimethylsilyl enolate (66) which

was then protonated in situ with trifluoroacetic acid. As expected, though its ratio was not high enough, the syn-epimer (68) was obtained as a major product in a 5.4:1 ratio and its structure was confirmed by conversion into (+)-citronellal (69) (Scheme 8).[26] In summary, I believe that construction of chiral tertiary and quaternary centers in the reflexion of the chirality of the "glycerol units" through a γ-lactone intermediate has reached the stage of practical applicability in the synthesis of a variety of natural products.

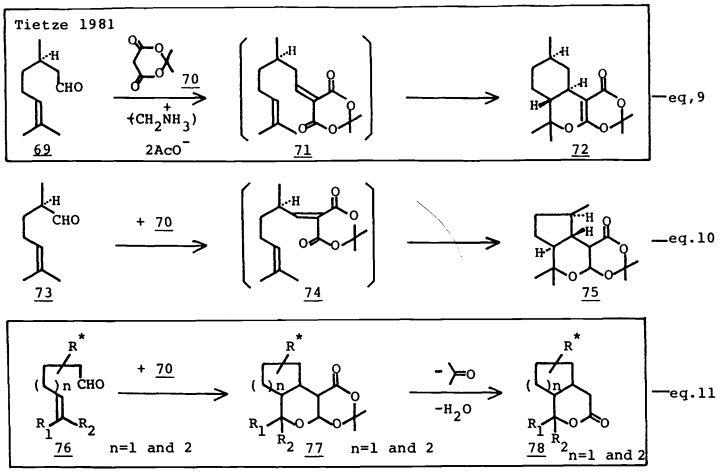
***Scheme 8***




## 2. SYNTHESIS VIA INTRAMOLECULAR HETERO-DIELS-ALDER REACTION

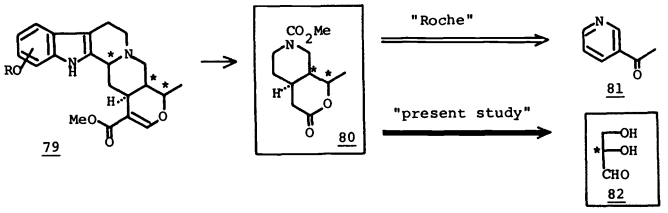
In 1981, Tietze reported an interesting reaction between citronellal (69) and Meldrum's acid (70) which gave a single compound with a trans 6/6 ring system selectively in 95% yield in one step via concomitant Knoevenagel type condensation and inverse electron demand intramolecular hetero-Diels-Alder reaction[27] (eq. 9). Stimulated by this finding, we tried the reaction between nor-citronellal (73) and Meldrum's acid (70) since we were very interested in whether it would form a trans 5/6 ring system which was expected to be more sterically compressed than the trans 6/6 ring system. The reaction proceeded very easily and the product obtained as a single epimer could be determined to be the trans 5/6 ring system (75) after degradation work[28] (eq. 10). At this

***Scheme 9***



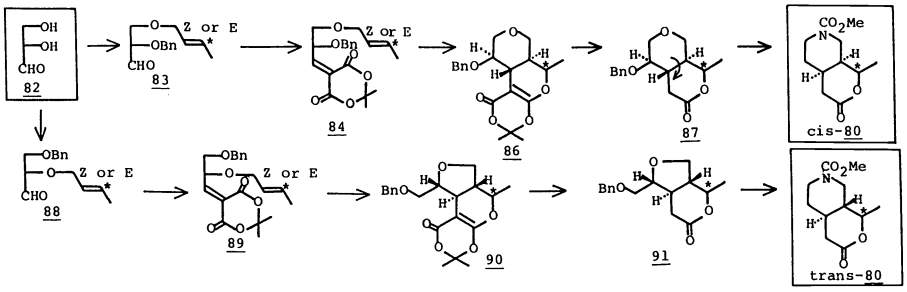

stage, we concluded that these two reactions allude the following stereochemical possibilities: 1) trans ring juncture is generated both in 6/6 and 5/6 ring systems, 2) chirality and position of the existing center controls chiralities of newly generated three consecutive chiral centers, and 3) chirality of the oxygen atom depends on the configuration of the olefin bond (eq. 11). In order to exploit these stereochemical features of the intramolecular hetero-Diels-Alder reaction in the utilization of the chiral "glycerol units", we first attempted the synthesis of the heteroyohimbine alkaloids (79) which contain three consecutive chiral centers in their molecules (Scheme 10). We chose four epimers of the bicyclic carbamates (80) as our immediate targets as two of them have already been synthesized from 3-acetylpyridine (81) employing microbial asymmetric reduction by the Roche group[29]

***Scheme 10***



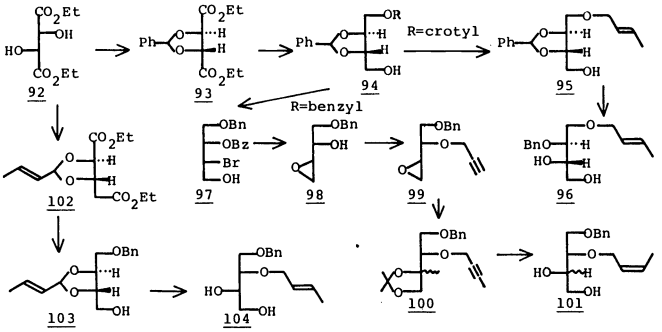
(Scheme 11). As shown in Scheme 11, we planned our synthesis starting with two pairs of isomeric di-O-substituted glyceraldehydes, (83) and (88), generated from a common "glycerol unit" (82).

***Scheme 11***

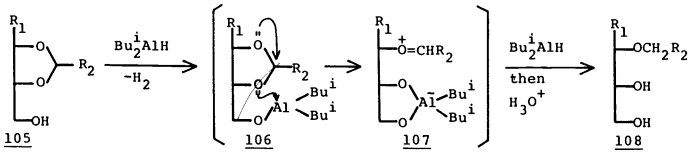


In practice, because selective functionalization of glyceraldehyde (82) itself is virtually impossible due to its instability, we used L-tartrate (92) as its equivalent (Scheme 12). Diethyl (L)-tartrate (92)was converted into the monocrotyl benzylidene acetal (95) employing standard conditions. We have already learned that diisobutylaluminum hydride (DIBAL) cleaves selectively at the proximal position to the hydroxy group during another experiment[30] and indeed the benzylidene acetal (95) afforded the single benzyl ether with a 1,2-glycol unit (96) selectively in good yield on treatment with DIBAL presumably due to the internal participation of the aluminum atom (Scheme 13).

***Scheme 12***



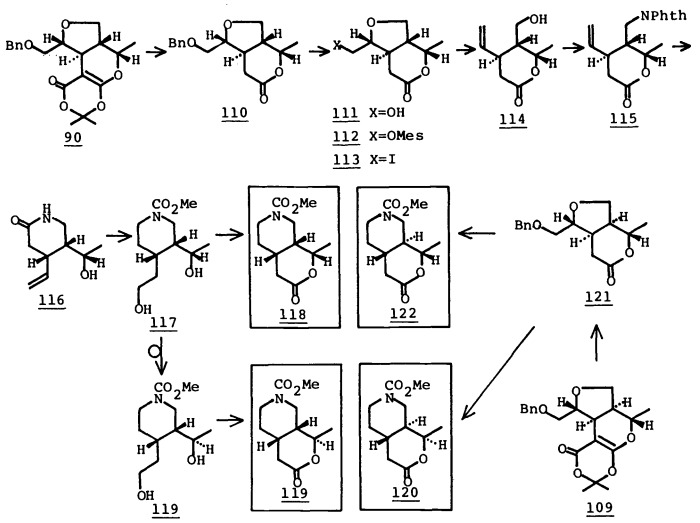
***Scheme 13***



On the other hand, the crotylidene monobenzyl ether (102), prepared in the standard manner, was similarly treated with DIBAL to give the 1,2-glycol with E-olefin (104), selectively. Although it took a little longer, the 1,2-glycol with Z-olefin (101) could also be obtained from the benzylidene monobenzyl ether (94 : R=Bn). In these conversions the epoxy alcohol (98) was obtained selectively by sequential treatment (94 : R=Bn) with NBS and methanolic potassium carbonate. Since the 1,2-glycol moiety is regarded as an equivalent of the formyl group, these conversions imply the synthesis of stable equivalents of the di-O-substituted glyceraldehydes which actually were converted to the corresponding glyceraldehyde upon cleavage with aqueous sodium periodate.

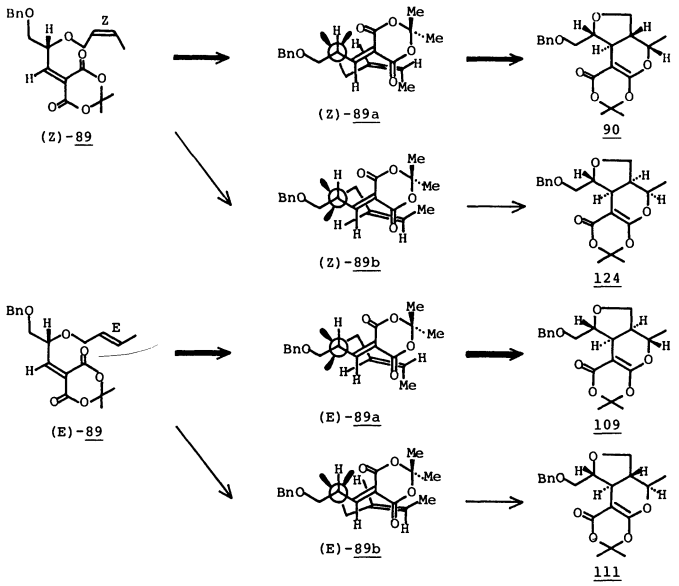
Having established the preparation of the requisite "glycerol units", we next attempted to react them with Meldrum's acid (70), respectively. All of the aldehydes reacted smoothly with the acid (70) at 0° to room temperature. We found that the 1-crotyl derivative (83) did not afford the expected tricyclic compound with a 6/6 ring system (86) but remained at the condensation stage (84), while both of the 2-crotyl derivatives (83) and (88) gave the corresponding tricyclic compounds both in stereoselective fashion which should have a trans 5/6 ring system (90). However, to our surprise, later conversion revealed both not to be isomeric at the carbon atom attached to the oxygen but at the ring junctures: the product generated from the Z-olefin (Z-88) was determined to be the expected trans-adduct (90), but the product generated from the E-olefin (E-88) was determined to be the unexpected cis-adduct (109). Structures of these adducts were determined by conversion into the bicyclic lactone carbamates, (118), (120), (122), and (123), as shown in Scheme 14.

***Scheme 14***




Thus, the trans-adduct (90) was converted into the bicyclic lactone (110) by heating in aqueous dioxane, which sequentially was converted into the diol (117) as shown. The diol (117) yielded the δ-lactone (118) excellently on heating with Fetizon reagent in benzene. On the other hand, chirality of the secondary hydroxy group of the diol (117) was inverted by employing the Mitsunobu's conditions to give the epimeric diol (119) which on Fetizon oxidation gave the epimeric δ-lactone (120). The enantiomer of this δ-lactone (120) has been already synthesized by the Roche group employing a completely different way; its spectral and physical data except for the sign of optical rotation correspond well with our compound. The same conversions were carried out on the adduct (109) obtained from the E-olefin (E)-(88) which should have furnished the same lactone carbamates (118) and (120) obtained from the adduct (90) from the Z-olefin (Z)-(88). However, the products obtained were not identical to those obtained from the Z-olefin suggesting that the former possessed a different ring fusion which could be confirmed by X-ray analysis of the compound (122). These results led us to conclude that the adduct (90) from the Z-olefin (Z)-(88) possessed the trans 5/6 ring system as expected, while the adduct (109) from the E-olefin (E)-(88) possessed the cis 5/6 ring system but not the expected trans system (111) in contrast with our initial expectation based on the assumption from the results of Tietze and our experiments. We believe that this striking difference is due to the interference between methyl groups on the dienophile and one of the isopropylidene group on the heterodiene in the transition states as shown in Scheme 15.[31]

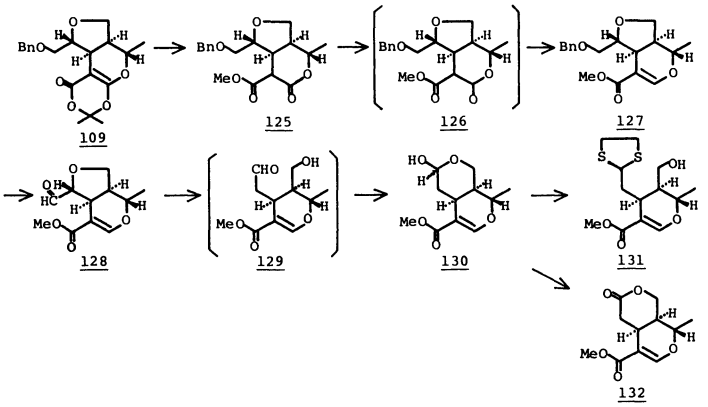
***Scheme 15***




Although the synthesis of four bicyclic carbamates formally constitutes an alternative chiral route to the heteroyohimbine alkaloids by employing the

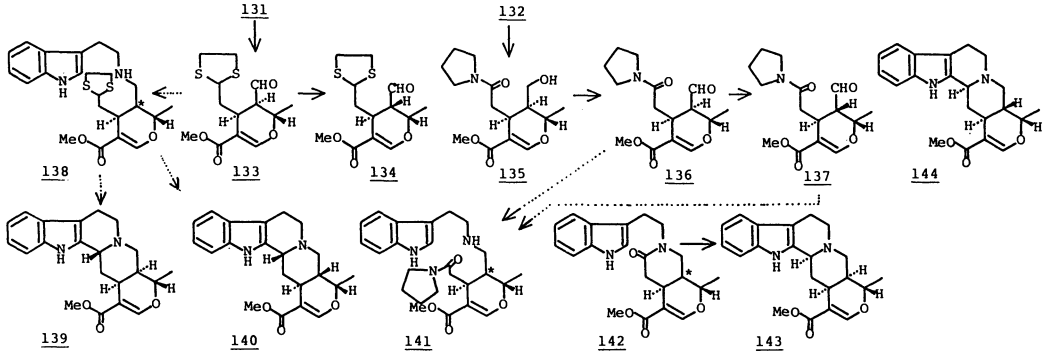
Roche synthesis, we sought a more facile route using the adduct (109) obtained from the E olefin (E)-(88). This route is easier than that via its Z-counterpart. Thus, the adduct (109) was converted into the acrylate (127) via chemoselective reduction of the ester (125) using lithium triethylborohydride followed by acid catalyzed dehydration. Reductive cleavage of the tetrahydrofuran ring of the aldehyde (128) obtained from (127) by oxidation was smoothly carried out by using Zinc in the presence of hydrochloric acid to give the hydroxy aldehyde (129) which was isolated as the hemiacetal (130). The hemiacetal (130) was converted into the thioacetal (131) in the presence of an equimolar amount of titanium tetrachloride, on the other hand, (130) was oxidized to the lactone (132) on treatment with Fetizon reagent (Scheme 16).

***Scheme 16***



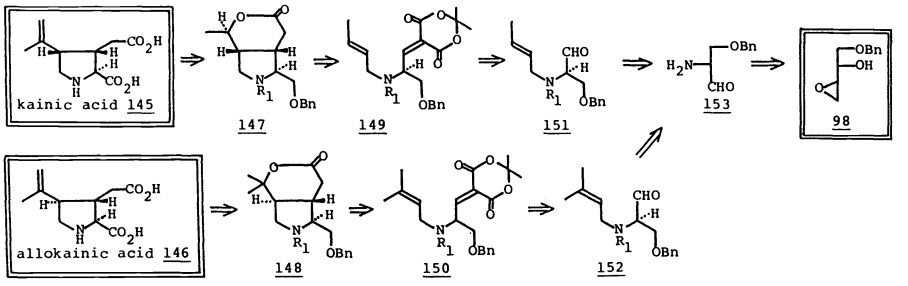
Oxidation of the thioacetal-acetal (131) gave the aldehyde (133) which was isomerized to the thermodynamically more stable trans epimer (134) on treatment with silica gel in methylene chloride. On the other hand, the lactone (132) was transformed into the amide (135) which could be similarly converted into the aldehydes (136) and (137).[32] Transformation of these aldehydes into the corresponding natural products, (139), (140), (143), and (144) is now under investigation (Scheme 17).

***Scheme 17***



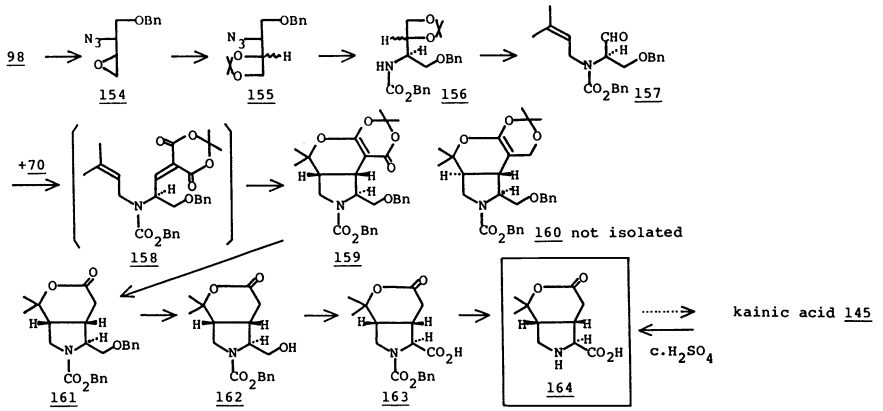
With the observed stereochemical outcome of the intramolecular cycloaddition, we turned our attention to the synthesis of kainic acid (145) and allokainic acid (146), which exhibit potent neuronal excitatory and insecticidal activities.[33] Retrosynthetic analysis of these compound with three consecutive chiral centers on a pyrrolidine framework led us to the epoxy alcohol (98) via the "aza-glycerol unit" (153) as a common starting material (Scheme 18).

***Scheme 18***



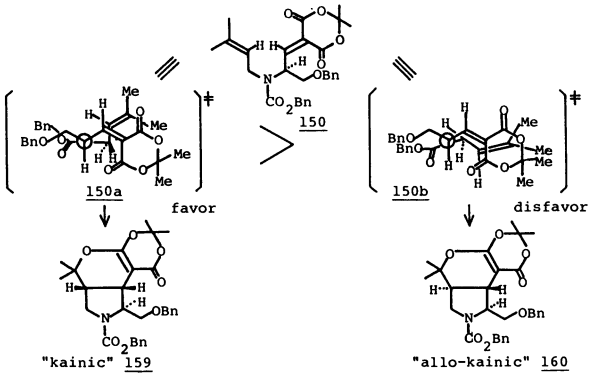
The epoxide (98) was converted into the carbamate (159) via the azide (154) as shown. We first prepared the prenyl derivative (157) from which we expected to obtain allokainic acid (146) since the trisubstituted olefin would give the 5/6 trans "allo" system as has already been shown (eq. 9 and 10). When the aldehyde (157) obtained from (156) was treated with Meldrum's acid (70), concurrent condensation and internal cycloaddition occurred at room temperature to give the tricyclic adduct (159) which was hydrolyzed to give the bicyclic lactone (161) as a single epimer. Since we could not determine the stereochemistry of the product, the lactone (161) was selectively debenzylated with boron tribromide to give the alcohol (162) which was then oxidized to the carboxylic acid (163) with Jones reagent. Debenzylation of the carboxylic acid (163) under hydrogenolytic conditions afforded the crystalline amino acid (164) which was found to be identical with the known compound obtainable from kainic acid (145) under acidic conditions (Scheme 19). This clearly

***Scheme 19***




indicated that the cycloaddition did not occur in the expected way to give the "allo" structure (160) but in a way to give the adduct (159) with cis-stereochemistry suitable for the synthesis of kainic acid (145) which is more attractive from the physiological point of view. We presumed that the unexpected stereochemical outcome may be attributable to the carbamate nitrogen the $sp^2$ nature of which disallows sufficient overlapping between the heterodiene and the dienophile in the molecule to generate the "allo" configuration (160) as shown in Scheme 20. We are now attempting to convert the amino acid (157) into kainic acid (145) which has not been accomplished and also to synthesize the related naturally occurring amino acids such as domoic acid and acromeric acids by exploiting the present findings.

***Scheme 20***




In conclusion, I believe that the "glycerol units", though they are the minimum chiral units, are extremely versatile chiral building blocks for the construction of a wide variety of optically active natural products as well as other optically active industrial materials.

**Acknowledgement**

I would like to express my sincere gratitude to my collaborator, Associate Professor Kunio Ogasawara, throughout the course of this work. I wish to express my cordial thanks to my coworkers whose names appear in the following papers. This research was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

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