Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 100, Nos 2 & 3, April 1988, pp. 91–111.

Synthetic approach to natural products by Claisen rearrangement of glyceraldehyde derivatives

TETSUJI KAMETANI*[1], HIROKO KASAI[1], ETSUKO SATO[2] and TOSHIO SUZUKI[2]

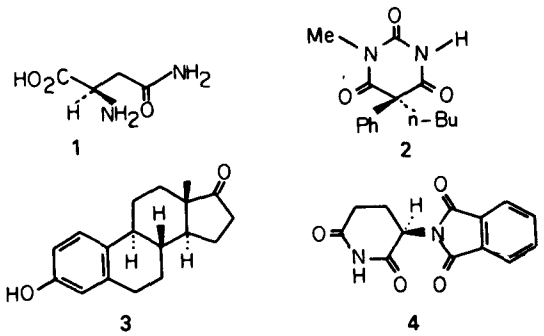
[1] Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

[2] Department of Pharmacy, Akita University Hospital, Hondo 1-1-1, Akita 010, Japan

Abstract. For the purpose of organic syntheses of some corynanthe-type indole alkaloids, sesquiterpenes, and steroids, optically active intermediates cyclopentanone 3-allylalcohol, α-methylene-γ-butylo lactones and *trans*-hydrindanone-propionic acid, were synthesized from (R)- and (S)-isopropylideneglyceraldehyde derived from D-mannitol and L-ascorbic acid, respectively, utilizing Claisen rearrangement as a key reaction. Actually total syntheses of natural alkaloids, (−)-antirhine, (+)-dihydroantirhine and (−) dihydrocorynantheol were accomplished.

Keywords. Chiral synthesis; sugars; Claisen rearrangement; Corynanthe-type indole alkaloid; sesquiterpene; steroid.

Some natural products and their enantiomers have differing characteristics from the biologically active point of view. Namely, one of them shows a biological activity while the other does not. For example, (R)-asparagine (1) is sweet, and (S)-one is not. (R)-Barbituric acid derivative (2) shows narcotism, while the (S)-one causes convulsions. (+)-Estrone (3) has female sex hormone activity, the (−)-one does not. (S)-Thalidomide (4) has a strong teratogenicity but the (R)-one does not.



1 2 3 4

Scheme 1

*For correspondence.

Chiral synthesis of the desired alternative isomer which has biological activity is one of the most active fields in organic syntheses at present. Generally, there are three synthetic methods for optically active compounds as given below:

(1) optical resolution;
(2) asymmetric synthesis;
(3) starting with optically active materials

Recently a number of biologically active compounds have been synthesized by utilizing methods (2) and (3). In case of method (3), sugar is often a suitable starting material because it is one of the cheapest and has 100% optical purity.

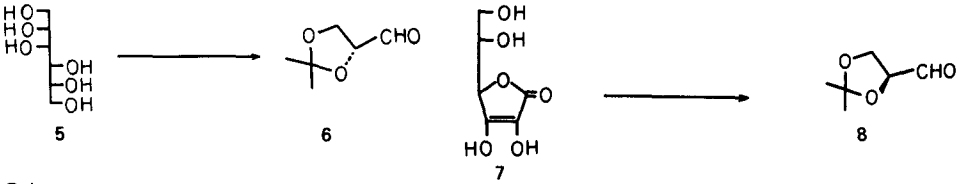
Though study of the organic synthesis of sugar was done even at the time of Emil Fischer (1852–1919) (Freudenberg 1966), sugar chemistry had been only a means for biological research work, and had not progressed rapidly because the properties of sugar make it not so easy to handle, for example, its water solubility and the difficulty in crystallizing it. But for the past ten years, superior protecting groups of the hydroxyl group have been developed; furthermore, the techniques of separation and purification and spectral analyses have progressed tremendously. Therefore sugar chemistry has also been progressing remarkably. As the result sugar has become an easy compound for dealing with as a starting material.

Presently, sugars attract our attention as the compounds which are directly concerned with vital phenomena such as nucleic acids or the substances determining blood-type. Moreover, from the asymmetric point of view, sugars are good optically active carbon sources because they are cheap and have various kinds of carbon-chains and definite absolute configurations.

The advantages of utilizing sugars as optically active materials are as follows.

(i) there is no need for optical resolution;
(ii) they are inexpensive and, moreover, have 100% optical purity
(iii) we can use various kinds of optically active carbon chains (mainly 3–6 carbon units);
(iv) conversions to (+)- or (−)-forms are so easy that sugars can be used in either form;
(v) reactions occur stereo- and regioselectively so that we can strictly retain the stereochemistry;
(vi) we can choose the desired type (pyranose, furanose, or normal chain type) from the same material as per our requirement.

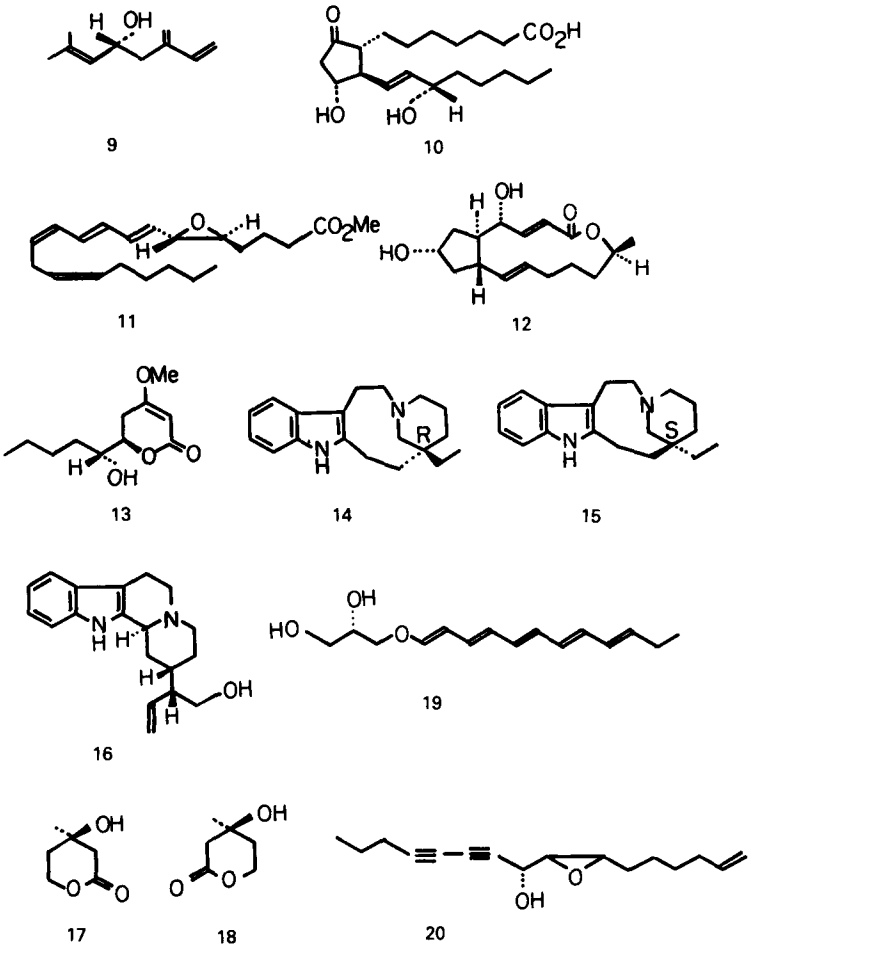
By making good use of these advantages mentioned above, research applying the chirality of sugars to the syntheses of natural products has been pursued vigorously, so that various kinds of natural products namely, low molecular compounds such as terpenoid and complex compounds such as macrolide or polyether has been synthesized successfully (Hanessian 1979; Ohuri 1981). (R)-1,2-isopropylideneglyceraldehyde (6) (Fischer and Baer 1934; Baer and Fischer 1939) obtained from D-mannitol (5) is widely utilized as starting material for synthesis of natural products, because of its asymmetric carbon atoms with hydroxyl groups and also because it is easy to synthesize 6 (2 equivalents) from 5 (1 equivalent). Further, its enantiomer, that is, (S)-1,2, isopropylideneglyceraldehyde (8) (Jung and Shaw 1980; Takano *et al* 1982) is obtained from L-ascorbic acid (7) easily.



5 6 7 8

Scheme 2 Scheme 3

For instance, natural products synthesized utilizing 6 as a starting material are as follows. (R)-(−)6-ipsdienol (9) (Mori *et al* 1979) which is an insect pheromone; prostaglandin E1 (10) Stork and Takahashi 1977) which attracts our attention because of its various kinds of biological activities; leucotriene A4 methyl ester (11) (Rokach *et al* 1981) brefeldin A (12) (Kitahara *et al* 1976) which shows a wide antibiotic spectrum; (+)-pestalotin (13) (Mori *et al* 1976) an enantiomer of (−)-pestalotin which is a gibbellin-synergist; (+)- and (−)-quebrachamine (14) (Takano *et al* 1980a) and (15) (Takano *et al* 1981d) which are aspidosperma-type iodole alkaloids; (−)-antirhine (16) (Takano *et al* 1981a, c), which is a corynanthe-

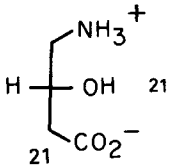


9 10 11 12 13 14 15 16 19 17 18 20

Scheme 4

type iodole alkaloid; (R)- and (S)-mevalonolactones (17 and 18) (Takano *et al* 1984) which are basic precursors for syntheses of various kinds of terpenes, steroids or alkaloids; (S)-3-(dodeca-1,3,5,7,9-pentaenyloxy)-propane-1,2-diol (19) (Nicolaou *et al* 1984) a mutagenic agent; and nematocical (20) (Sugiyama and Yamashita 1980) isolated from *Cirsium japosium*.

On the other hand, a synthetic example utilizing 8 as starting material is (−)-γ-amino-β-hydroxylbutyric acid (21) (Jung and Shaw 1980) which is effective in the treatment of arteriosclerosis.



Scheme 5

Claisen rearrangement, a method of forming a new C–C_δ bond together with the removal of the double bond by thermodynamic [3·3]sigmatropic rearrangement of allyl vinyl ether (22–23), (Claisen 1912) is an effective means of asymmetric synthesis and this rearrangement has been used for the stereoselective syntheses of various kinds of natural products (Ziegler 1977; Nakai *et al* 1983).

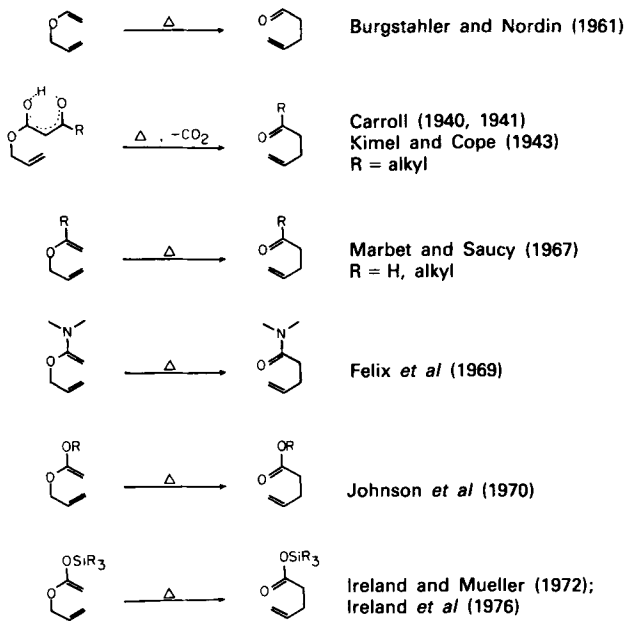
Scheme 6

Representative synthetic routes known so far are shown in scheme 7. For instance, unsaturated aldehydes, ketones, amides, esters, or carbonic acids were synthesized. This rearrangement occurred on heating between room temperature and 200°C.

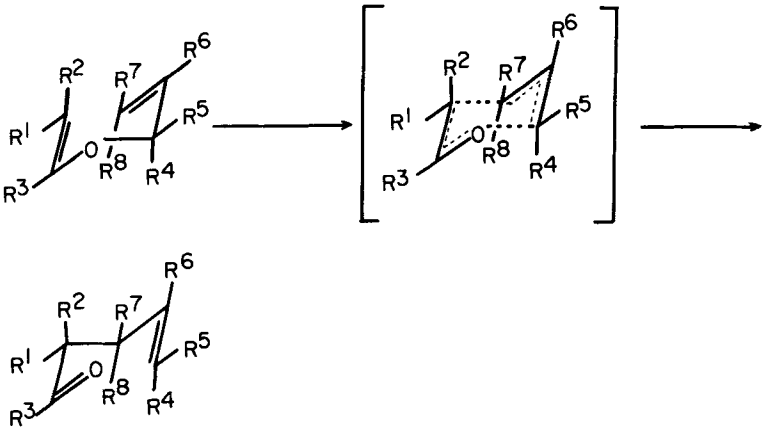
Stereochemistry in Claisen rearrangement was examined circumstantially by the basic research work of pioneers such as von Doering and Roth (1962), Vittorelli *et al* (1975), Hansen and Schmid (1974), Hill and Gilman (1967) and Faulkner and Peterson (1969). As a result, it was clarified that the [3·3]sigmatropic rearrangement is advanced through a six-membered chair conformation that has the least steric hindrance, and a geometric isomerism of the newly formed double bond is *E* form selectively.

Furthermore, the stereochemical characteristics of the asymmetric center are widely utilized for syntheses of natural products Sucrow and Girgensohn 1970; Bolton *et al* 1971; Sucrow *et al* 1973; Chan *et al* 1976; Stork and Raucher 1976; Lythgoe *et al* 1977; Stork and Takahashi 1978; Stork *et al* 1978; Ireland *et al* 1980; Koreeda *et al* 1980; Tanabe and Hayashi 1980; Grieco *et al* 1981; Takahashi 1981, 1982; Martinez *et al* 1982) and several representative examples are shown in schemes 9 and 10.

Stork *et al* (1978) synthesized PGF_2 α (26) utilizing glucose as the starting material. Orthoester Claisen rearrangement of allyl alcohol (24) shifts the chiral



Scheme 7

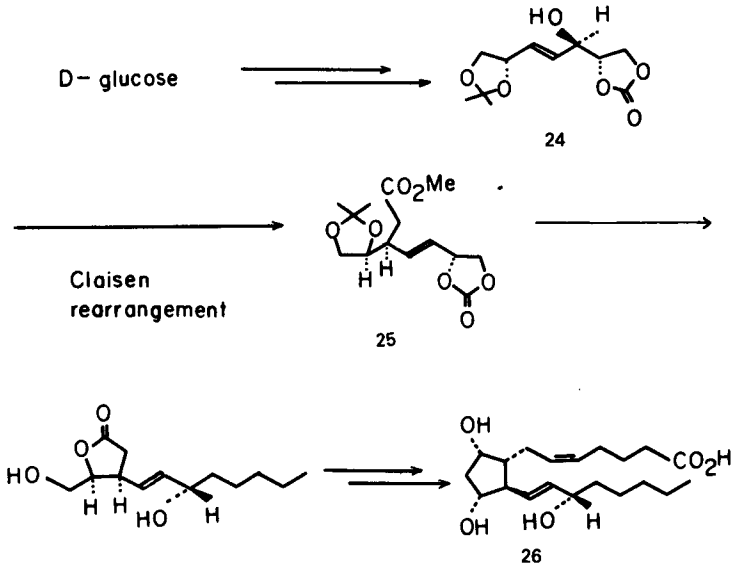


Scheme 8

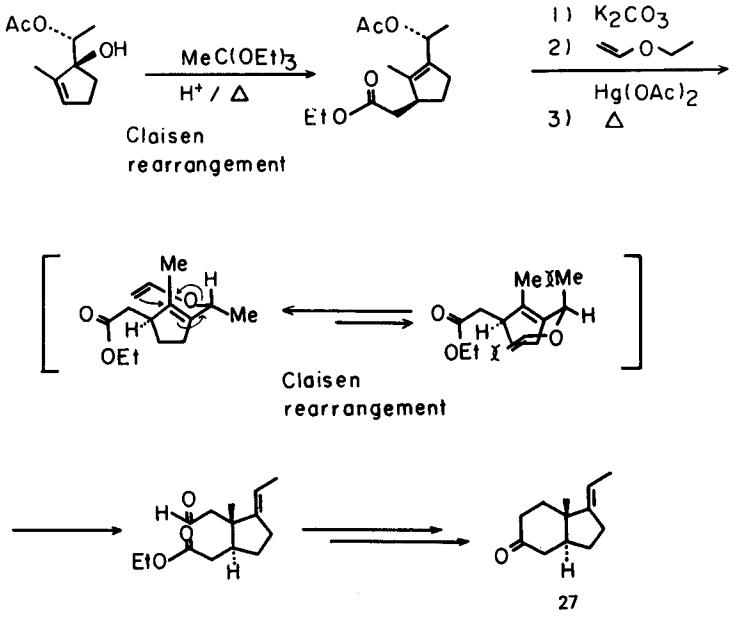
center from C–O to C–C, and the resulting compound (25) has a stereocontrolled C–12 position together with *trans*-olefin at C–13, 14 positions which are indispensable to 26.

Takahashi *et al* (1981, 1982) achieved a synthesis of de-AB-cholestan-9-one (27) utilizing the Claisen rearrangement twice. The *trans*-indane skeleton is essential for stereocontrolled synthesis of the steroid skeleton.

Utilizing the Claisen rearrangement mentioned above as a key reaction, we synthesized some compounds from 6 or 8 such as (−)-antirhine (16), (+)-dihydroantirhine (28) and (−)-dihydrocorynantheol (29), which are Corynanthe-

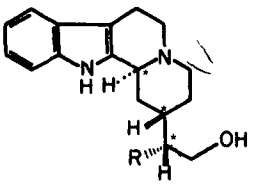


Scheme 9



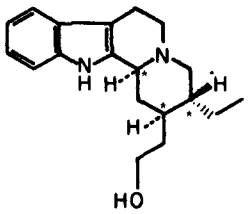
Scheme 10

type indole alkaloids, α-methylene-γ-butylolactones (30 and 31), which are the important intermediates in the syntheses of sesquiterpenes, *trans*-hydrindanone-propionic acid (32), which is a significant intermediate in the synthesis of 11-keto steroids. Detailed accounts of these are given below.

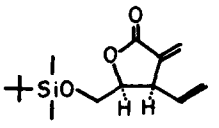


16: R=CH=CH$_2$

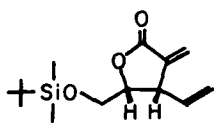
28: R=Et



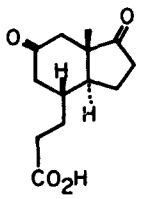
29



30



31



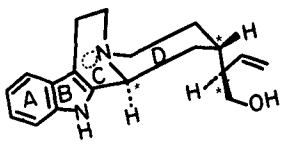
32

Scheme 11

Corynanthe-type indole alkaloids

(−)-Antirhine (16) (mp 112–114°C, $[\alpha]_D$-2° ($CHCl_3$)) was isolated from *Antirhea putaminosa* leaves by Johns *et al* (1967). The hydrogen at the C–15 position of corynanthe-type indole alkaloids, is generally located at the α-position but antirhine is one of a small number of such compounds which has the C–15 hydrogen in the β-position.

Further, antirhine has a C/D *cis* conformation, three asymmetric carbons at the C–3, C–15, C–20 positions, and vinyl and hydroxyl groups at the C–20 position, which is an attractive construction.

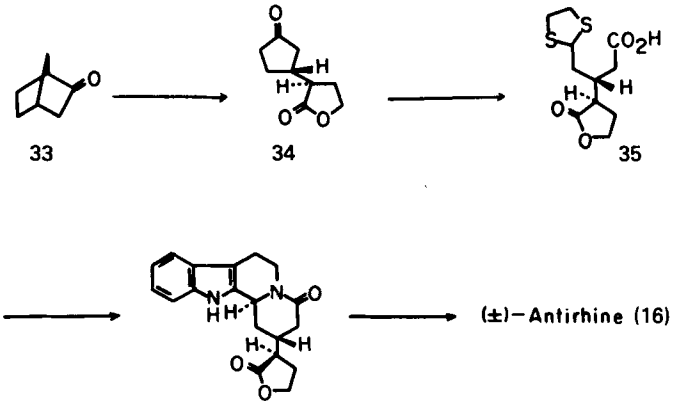


16

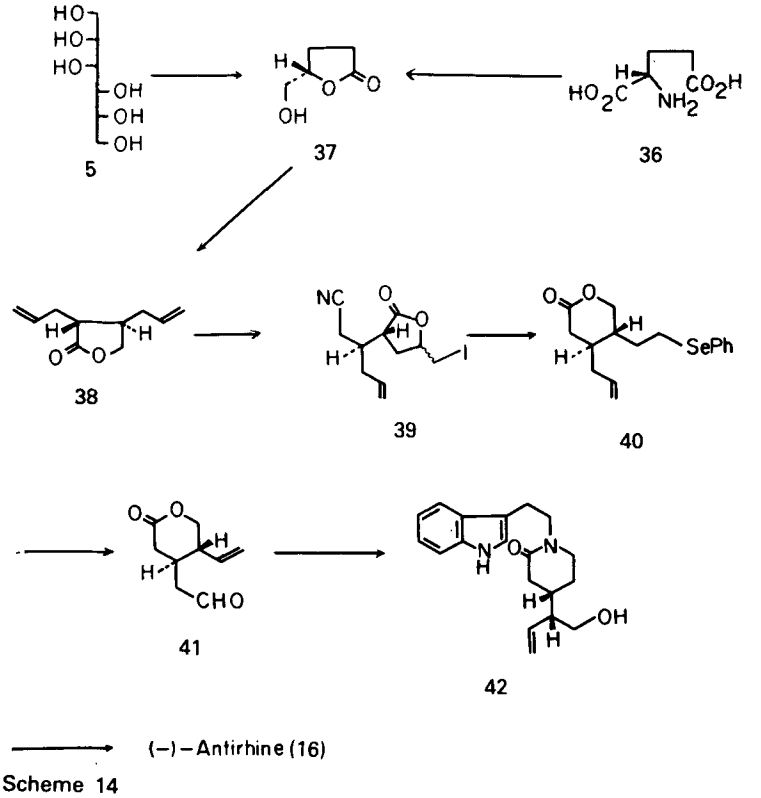
Scheme 12

Takano *et al* (1980a) synthesized (±)- and (−)-16. The five-membered ring of γ-lactone (34) obtained from (±)-norcamphor (33) stereoselectively was cleaved by Marshall's method to give the compound (35), which was converted to (±)-16 by

activation of the carboxylic acid group with methylchlorocarbonate and subsequent condensation with tryptamine. On the other hand, in the case of (−)-16, the chiral lactone (37) obtained from D-mannitol (5) or L-glutamic acid (36), was alkylated stereoselectively to give *trans*-diallyl-lactone (38), which led to the desired final compound through introduction of a nitrile group and subsequent halolactonation of the carboxylic acid group (Takano *et al* 1981d).



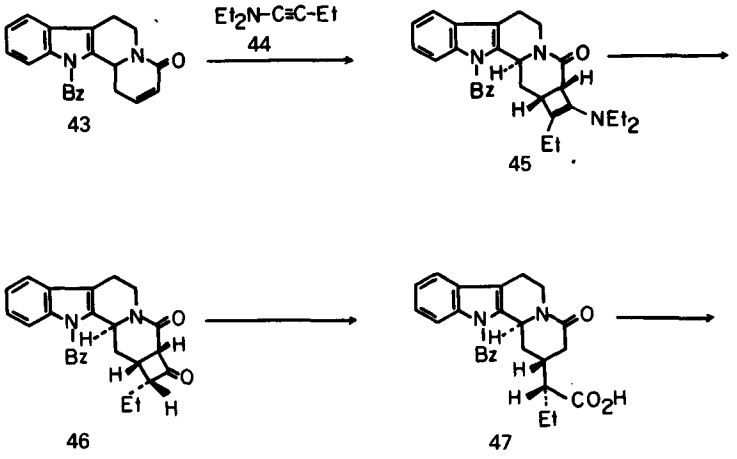
Scheme 13



Scheme 14

(+)-Dihydroantirhine (28) (Johns *et al* 1967) (mp 106–108°, $[\alpha]_D$ + 23 (c = 0·12, $CHCl_3$), $C_{19}H_{26}N_2O$ (m/z 298)), obtained through hydrogenation of (−)-16 with Adams' platinum, is an isomer of dihydrocorynantheol (29) or corynanthediol with are Corynane (17,18-secoyohimbane)-type alkaloids.

Several methods for synthesis of (±)-28 have been reported by some groups already (Sawa and Matsumura 1969; Kimura and Ban 1969; Wenkert *et al* 1973; Chevolet *et al* 1975; Fucini *et al* 1979). Among them the route elucidated by Fucini *et al* (1979) is the most attractive, because the stereochemistry of the C–3, C–15 and C–20 positions were controlled. Thus cycloaddition of the unsaturated lactam (43) to the inamine (44) gave enamine (45) stereocontrolled at the C–3 and C–15 positions. On subsequent hydrolysis, hydrogen was attacked from the less-hindered *exo*-side, so that the C–15 and C–20 positions were controlled to give 46, through 47, and the desired (±)-28 was finally obtained.

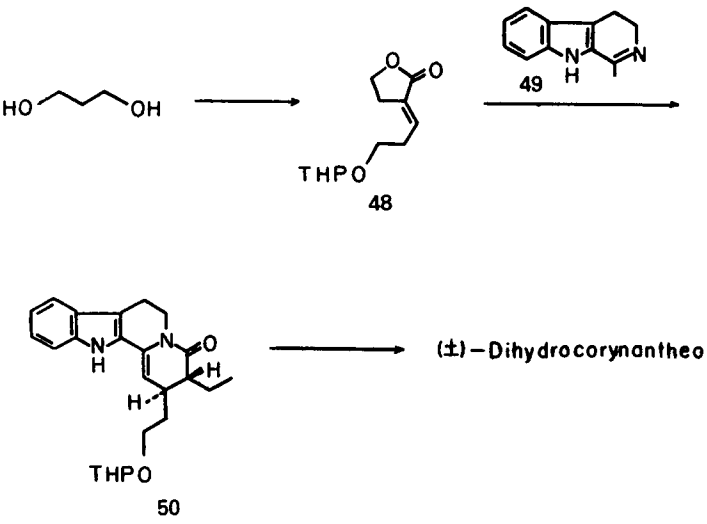


Scheme 15

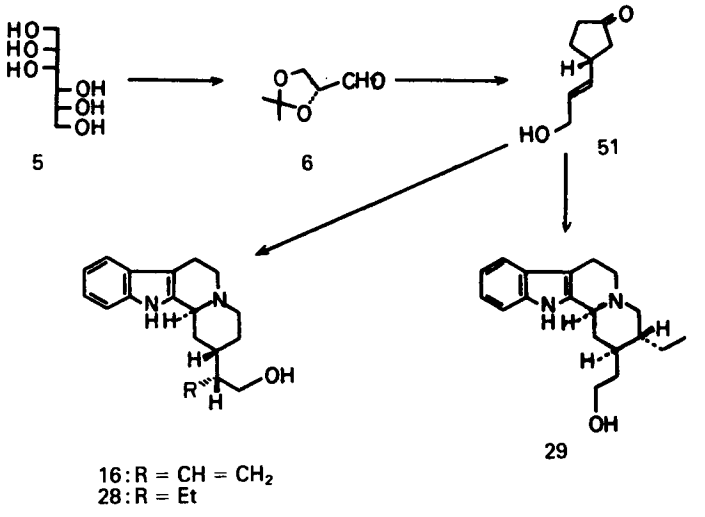
(−)-Dihydrocorynantheol (29) (mp 181–183°C, $[\alpha]_D$-19° (c = 1·02, $CHCl_3$), $C_{19}H_{26}N_2O$) was isolated from the bark of the Amazonian tree *Aspidosperma marcgravianum* Woodson by Gilbert *et al* (1962).

Some methods of synthesis of (±)-29 have been reported by several groups (Vamvacas *et al* 1957; Ziegler and Sweeny 1969; Kametani *et al* 1980; Takano *et al* 1981b; Danieli *et al* 1984). Among these Danieli's route (Danieli *et al* 1984) utilizing enamine annulation of 48 with 49 is very interesting.

As mentioned earlier, optically active (−)-antirhine (16) has been already synthesized by the Takano group, while optically active (+)-dihydroantirhine (28) and (−)-dihydrocorynantheol (29) have not been synthesized yet. So we tried to synthesize these compounds (16, 28 and 29) utilizing the common intermediate (51) obtained from 6 using D-mannitol (5) as the starting material.

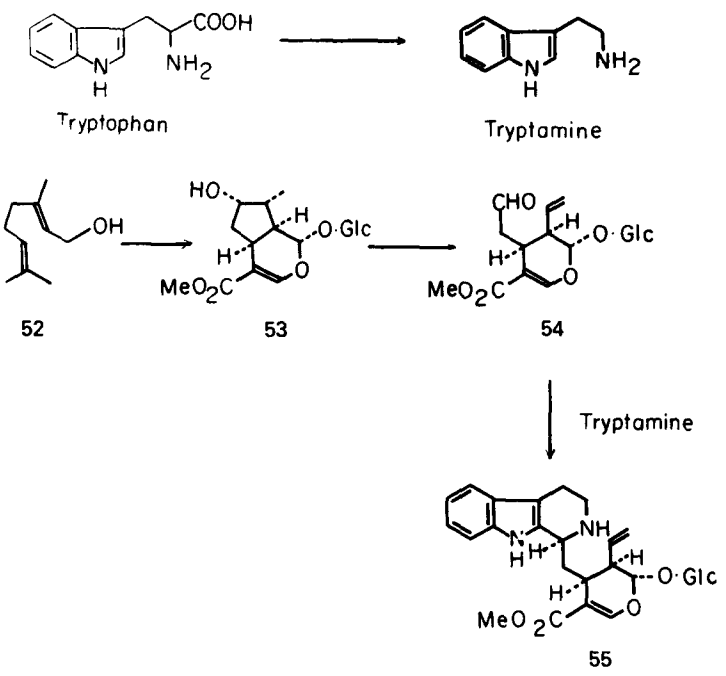


Scheme 16



Scheme 17

In general, indole alkaloids consist of a tryptamine and a non-tryptamine part. The hypothesis that the tryptamine part is obtained by decarboxylation of tryptophan and the non-tryptamine part is derived from monoterpene has been proved correct by many tracer-experiments (Battersby *et al* 1966, 1968; Battersby 1967; Loew and Arigoni 1968; Burnett and Parsons 1968, 1969). Based upon it, it was clarified that the non-tryptamine part (C_9–C_{10} unit) is derived from geraniol (52) (Chain-type monoterpene). Loganine (53) obtained by cyclization of 52 is changed to secologanin (54) and subsequent condensation with tryptamine gives isovincoside (55), which is used in a number of indole alkaloids.



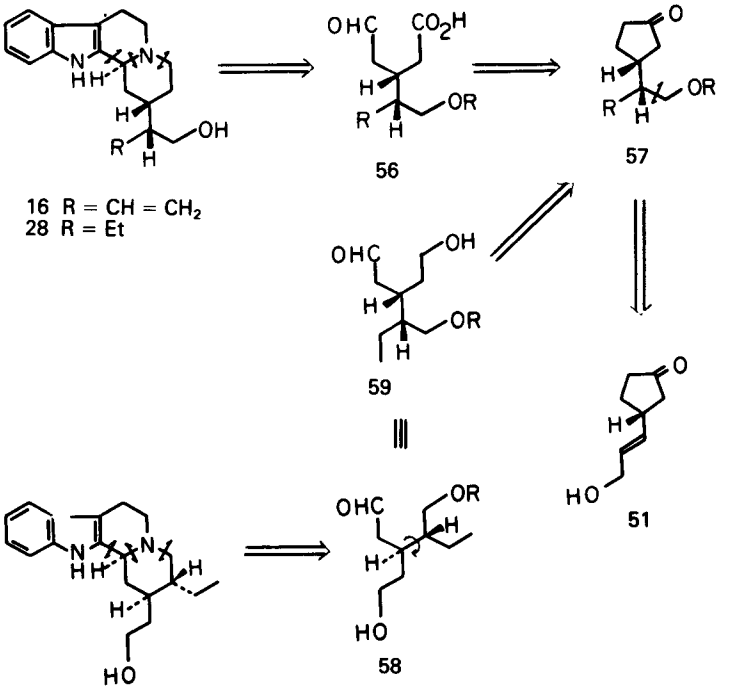
Scheme 18

From a synthetic point of view it is possible that various kinds of indole alkaloids are synthesized from the common chiral precursor. If the synthetic routes of 16, 28 and 29 are as shown in scheme 19, cyclopentanone 3-allylalcohol (51) is assumed to be the common chiral precursor. Namely compound (56) is supposed to be a precursor of the non-tryptamine part of 16 and 28. Compound (56) was obtained from 57 (derived from 51 by rearrangement) through thioacetalization of 57 and a subsequent ring-opening reaction.

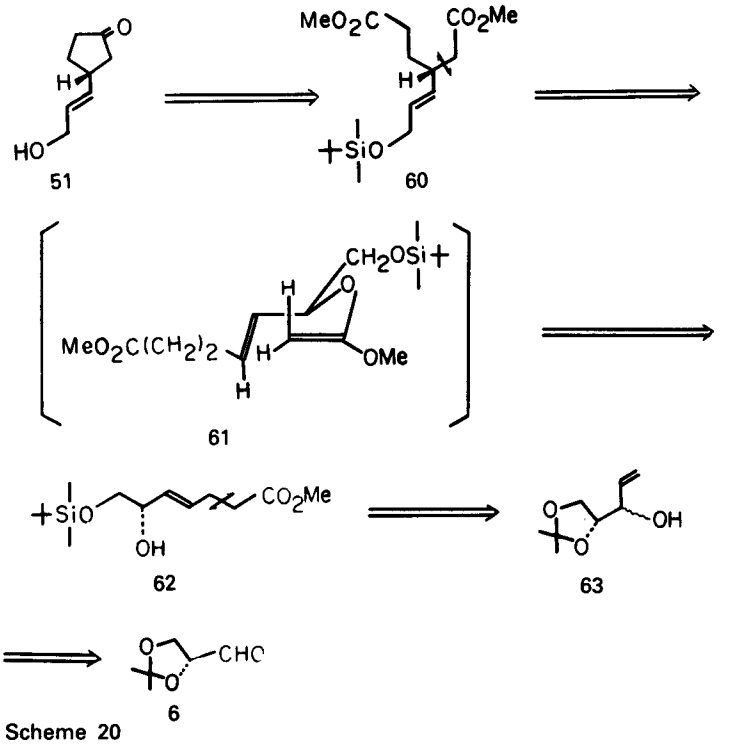
On the other hand, compound 58 which is equivalent to 59 is supposed to be a precursor of the non-tryptamine part of 29. So we decided to synthesize the cyclopentanone (51), a common intermediate in the syntheses of 16, 28 and 29. Compound (51) can be synthesized by Dieckmann reaction of 60 obtained through double Claisen rearrangement of 62 derived from 63, which is obtained by Grignard reaction of 6. The key reaction of a rearrangement of a chiral center from the C–6 position of 62 to the C–4 position of 60 can be accomplished by Claisen rearrangement with trimethyl orthoacetate through 61 as an intermediate.

Under the considerations mentioned above we synthesized (3R)-[3-hydroxy-(E)-prop-1-enyl]cyclopentanone (51) (Kametani *et al* 1982a) from (R)-1,2-isopropylideneglyceraldehyde (6).

Further, on the basis of the above consideration, we accomplished the total synthesis of (−)-antirhine (16), (Suzuki *et al* 1986d), (+)-dihydroantirhine (28) (Kametani *et al* 1982b) and (−)-dihydrocorynantheol (29) (Suzuki *et al* 1986a) from the common key intermediate (51). Namely 64 was obtained by 2,3-sigmatropic rearrangement, introducing a C_1 unit into 51. Compounds (65 and 66), derived through hydrolysis of 64, were converted into 67 and 68 respectively. Selective

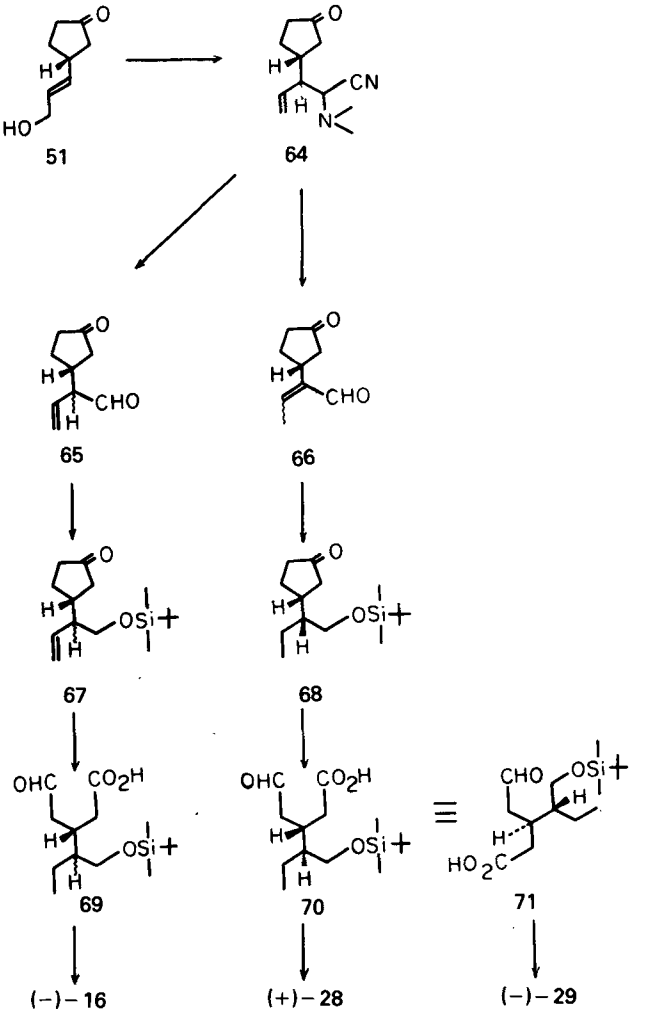


Scheme 19



Scheme 20

five-membered ring opening reaction gave 69 and 70, which were condensed with tryptamine respectively to give (−)-16 and (+)-28. On the other hand 70 is equal to 71, and (−)-29 was obtained by condensation of 71 with tryptamine.

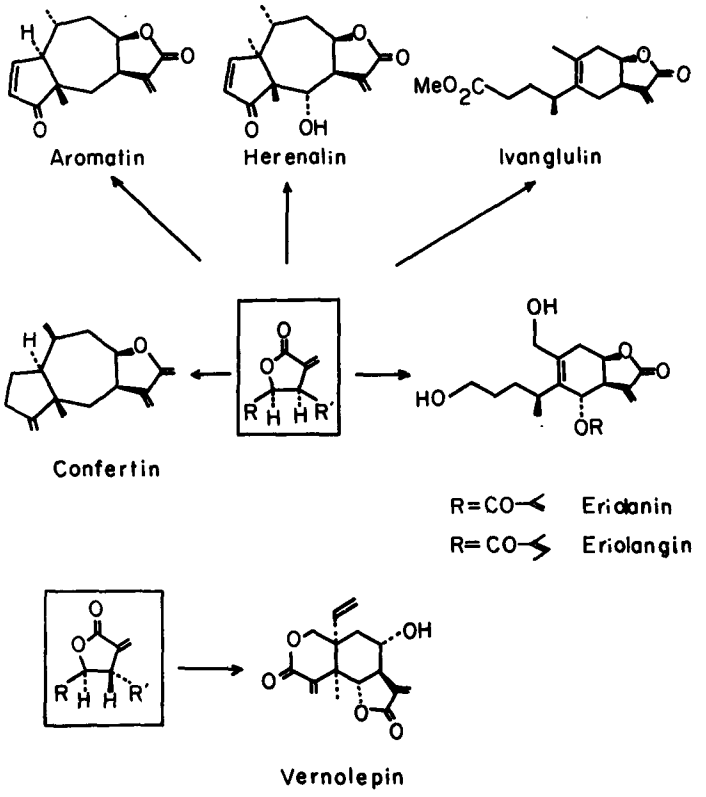


Scheme 21

Sesquiterpenes

Sesquiterpene, a general term for a terpene composed of 15 carbon atoms, has various biological activities. From a structural point of view, there are different kinds of skeleton-types, all structurally attractive. Vernolepin, isolated and characterised by Kupchan *et al* (1968), has anti-tumor activity, and as soon as the theory (Kupchan *et al* 1970; Lee *et al* 1977) that its biological activity would be revealed by alkylation through Michael reaction of the α-methylene-γ-butylolactone ring with cysteine-residue of enzyme was proposed, the syntheses of

sesquiterpenes with the ring were examined keenly (Grieco 1975; Gammil *et al* 1975; Newaz 1977; Shono and Matsumara 1981). To date it is known that there are four types of α-methylene-γ-butylolactone rings as shown in scheme 22. For the purpose of syntheses of sesquiterpenes, a stereoselective synthetic route of 2,3-substituted α-methylene-γ-butylolactones should be established.

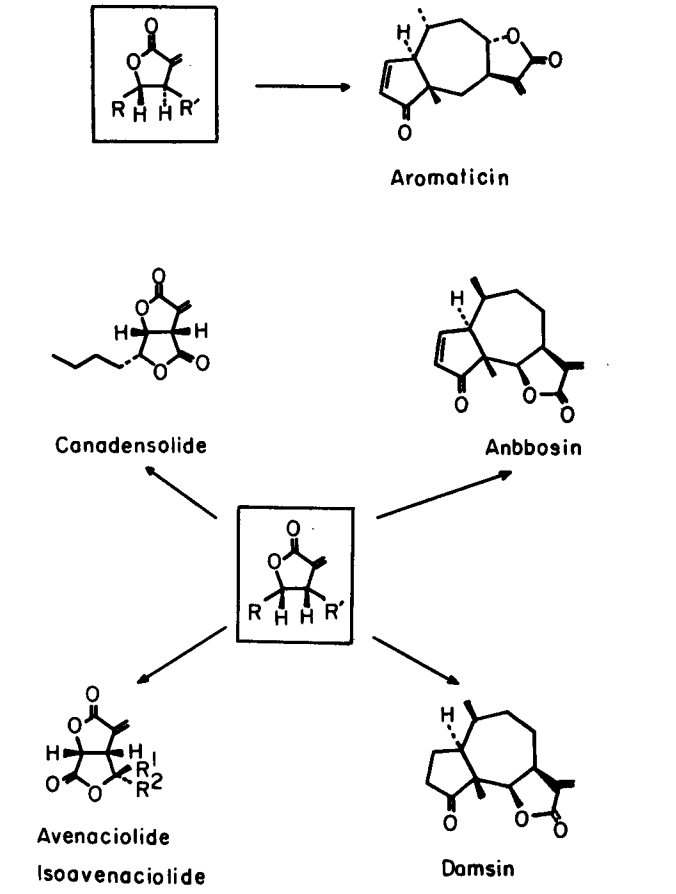


Scheme 22-1

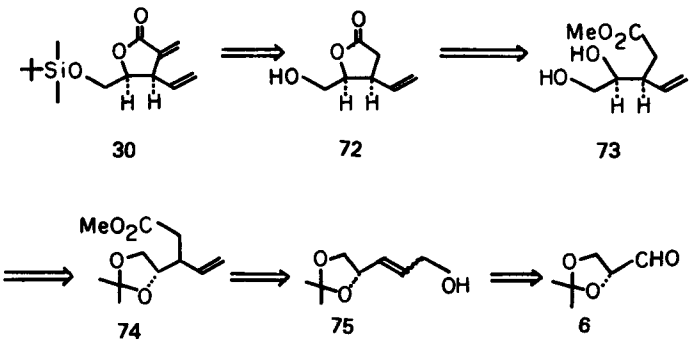
Among these lactones we investigated stereoselective syntheses of 2α, 3α- and 2β, 3β-substituted γ-lactones (30 and 31), the basic structures of many natural products. First of all we studied different methods of synthesizing them. For instance, compound (72), a precursor of 2α, 3α-γ-lactone (30) can be obtained by ring-closing reaction of 73 derived from 74. The acetal (74) can be synthesized from 75 through Claisen rearrangement being attacked from the less-hindered β-face, utilizing 6. On the other hand, 2α, 3β-γ-lactone (31), enantiomer of 30, can be derived from 8 by the same way. On above basis we established the synthetic routes of 30 and 31 (Kametani *et al* 1986).

Steroids

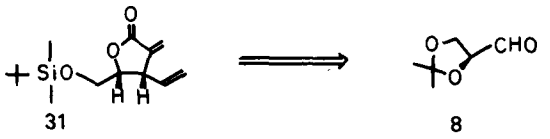
Steroids, a general term for a compound which has a cyclopentanoper-hydrophenanthrene skeleton (B/C *trans*, C/D *trans*) consists of three six-membered rings



Scheme 22-2



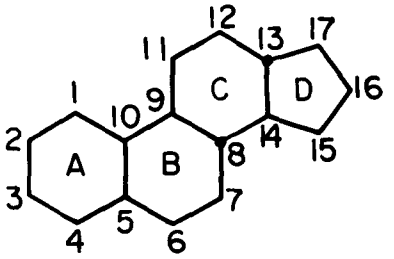
Scheme 23



31 8

Scheme 24

and a five-membered ring. In the case of natural products two methyl groups are located at the 10- and 13- positions, and a carbon chain at the 17- position, and the compounds generally have 18 ~ 29 carbon atoms.



Scheme 25

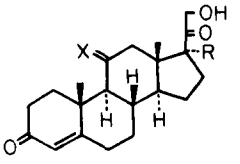
Steroids play an important role in metabolism. For example, sexual hormones (such as estrogens, gestagens, androgens and adrenocortical hormones), active vitamin D, bile acid etc. are steroids and they have an important influence upon life and health. A shortage or abnormal secretion of these cause many kinds of illnesses, and hence they are indispensable for medical treatment. Natural steroids, such as cardiac glycosides being used as diuretics, and also as choleretics, antihypertensive agents or antiatherosclerosis agents are well known. Furthermore, some of the effective ingredients of Chinese traditional medicines or crude drugs used for folk remedies belong to the steroid group. Steroids are expected to be helpful for medical treatment. Among these natural steroids the adrenocortical hormones play a part in some biological activities such as gluconeogenesis, anti-inflammation, immunosuppression, and anti-allergy, and are now utilized widely in medicine.

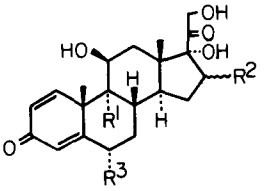
In 1935 and 1936 Wintersteiner (Pfiffner *et al* 1935; Wintersteiner and Pfiffner 1935, 1936) Reichstein (Reichstein 1936, 1937; Steiger and Reichstein 1937, Reichstein and Fuw 1938) and Kendall (Mason *et al* 1936a, b) isolated successively cortisone (76a), cortisol (76b), and corticosterone (76c) as crystals and elucidated their structures.

Sarett (1946) synthesized cortisones for the first time utilizing deoxycholic acid as starting material. Subsequently in 1949 Hench proved its dramatic effect in the treatment of rheumatoid arthritis, so that it became the object of public attention.

In consequence, studies relating to reference or conversion-reactions of natural steroids were carried out energetically, and much effort was put in to increase their useful effects such as glucose-metabolism, anti-inflammation, and anti-allergy, and to decrease their harmful effects such as diuresis, so that synthetic steroids,

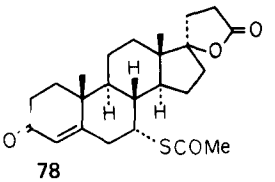
predonisolone (77a), methyl predonisolone (77b), triamcinolone (77c), dexamethasone (77d), betamethasone (77e) and spironolactone (78) were developed.





76 a X=O , R=OH
76 b X=β-OH , R=OH
76 c X=β-OH , R=H

76 a $R^1=R^2=R^3=H$
76 b $R^1=R^2=H$, $R^3=Me$
76 c $R^1=F$, $R^2=\alpha$-OH, $R^3=H$
76 d $R^1=F$, $R^2=\alpha$-Me, $R^3=H$
76 e $R^1=F$, $R^2=\beta$-Me, $R^3=H$

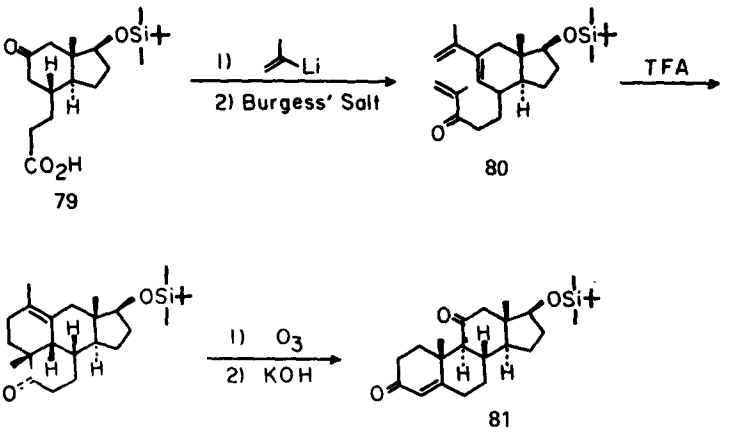


78

Scheme 26

As mentioned above steroids have various kinds of biological activities and possess interesting structures and hence, their total syntheses became an important target of great interest for chemists. Synthetic routes of steroids reported to date are classified into two large groups. One is the synthesis of the steroid skeleton (A,B,C,D-rings), the other is the introduction of the steroid side chain (Piatak and Wicha 1978; Takahashi *et al* 1982; Redpath and Zeelen 1983) into available natural steroids. Typical examples of the former are the Robinson annulation (Gawley 1976; Jung 1976; Blickenstaff *et al* 1974; Cohen 1976) of biomimetic cyclization (Johnson 1976; Sutherland 1980; Bartlett 1984; Van Tamelen 1986) for testosterone, the intramolecular Diels-Alder reaction (Oppolzer 1978; Kametani 1979; Funk and Vollhardt 1980) of *o*-quinodimethane for estrone, and the reductive alkylation (Stork and Logusch 1980) of ene-dione or the intramolecular Diels-Alder reaction (Stork *et al* 1981) for cortisone.

In 1981 as soon as Stork *et al* (1981) synthesized 11-keto steroid (81) utilizing the intramolecular Diels-Alder reaction of 80 derived from the keto acid (79), compound (79) and relative compounds were observed to be important intermediates. Several methods for synthesizing them were reported (Stevens and Gaeta 1977; Trost *et al* 1979; Grieco *et al* 1979; Jung and Halweg 1981; Kametani *et al* 1982; Stork and Sherman 1982; Stork *et al* 1982, 1983, 1984; Wilson and Haque 1982, 1983; Stork and Kahne 1983; Snider and Kirk 1983; Desmaële *et al* 1983; Denmark and Germanas 1984; Fukuzaki *et al* 1984; Takahashi *et al* 1984; Hutchinson *et al* 1984; Ziegler and Lin 1984; Nemato *et al* 1985).

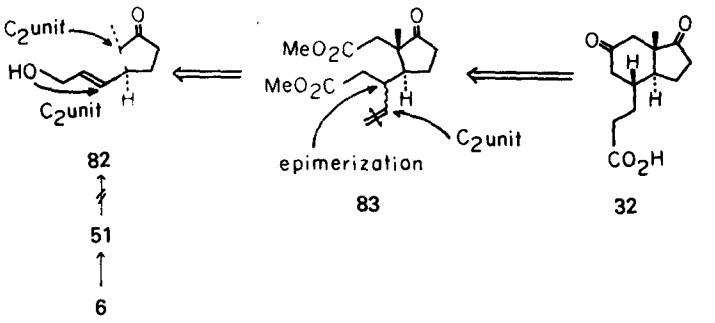


79 80 81

Scheme 27

Though a number of synthetic routes were reported, synthetic methods making use of sugars as starting material has never been reported yet. So we tried to convert (*R*)-1,2-isopropylideneglyceraldehyde (6) into *trans*-hydrindanonepropionic acid (32), an important intermediate in the syntheses of 11-keto steroids such as cortisone (76a)

First of all we examined its synthetic route. Regioselective introduction of a methyl group at the C-2 position of cyclopentanone (51) derived from 6 was supposed to give 82. Then a C_2-unit, necessary for the formation of the C-ring, was introduced at the C-2 position of 82 stereoselectively, and by subsequent orthoester Claisen rearrangement with trimethyl orthoacetate, the vinyl groups needed for the formation of A,B-rings were introduced to give 83. After the formation of a C-ring followed by cleavage of the double bond, the aldehyde group of the resultant compound was epimerized to an α-position. Subsequent introduction of a C_2-unit with methyl (triphenylphosphoranylidene)acetate, followed by hydrogenation of the unsaturated double bond led to the propionic acid (32), though actually conversion of 51 into 82 did not proceed with satisfactory yield.

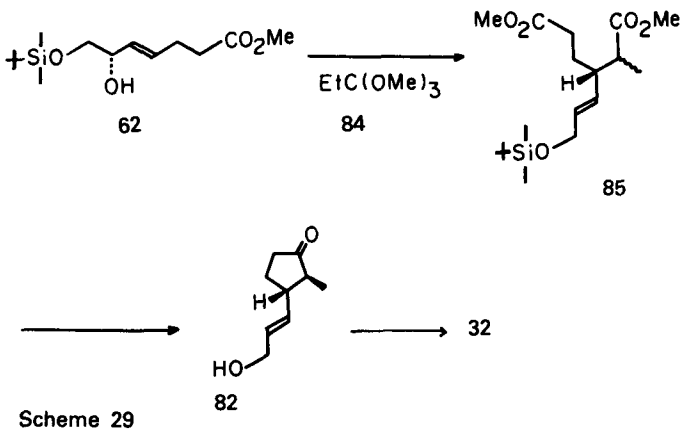


82 51 6 83 32

Scheme 28

Thus compound (82) was synthesized as follows. By Claisen rearrangement of 62 with trimethyl orthopropionate (84), the dimethyl ester (85) which has a methyl

group at the C-1 position was obtained. Subsequent Dieckmann reaction followed by decarboxylation gave the desired 2-methylcyclopentanone (82) successfully.



Scheme 29

Continuing, according to the above synthetic route (shown in scheme 28), *trans*-hydrindanonepropionic acid (32) (Suzuki *et al* 1986c), an important intermediate for 11-keto steroidal synthesis, was obtained from 82.

References

Baer E and Fischer H 1939 *J. Biol. Chem.* **128** 463
Bartlett P A 1984 *Asymmetric synthesis* (New York: Academic Press) vol.3, p. 341
Battersby A R, 1967 *Pure Appl. Chem.* **14** 177
Battersby A R, Brown R T, Kapil R S, Martin J A and Plunkett A O 1966 *Chem. Commun.* 890
Battersby A R, Kapil R S, Martin J A and Mo L 1968 *Chem. Commun.* 133
Blickenstaff R T, Ghosh A C and Wolf G C 1974 *Total synthesis of steroids* (New York: Academic Press)
Bolton I J, Harrison R G and Lythgoe B 1971 *J. Chem. Soc. C.* 2950
Burgstahler A W and Nordin I C 1961 *J. Am. Chem. Soc.* **83** 198
Burnett A R and Parsons P G 1968 *Chem. Commun.* 1280
Burnett A R and Parsons P G 1969 *J. Chem. Soc. C.* 1187
Carroll M F 1940 *J. Chem. Soc.* 704, 1266
Carroll M F 1941 *J. Chem. Soc.* 507
Chan K K, Cohen N, DeNoble J P, Specian A C Jr and Saucy G 1976 *J. Org. Chem.* **41** 3497
Chevolet L, Husson H P and Potier P 1975 *Tetrahedron* **31** 2491
Claisen L 1912 *Chem. Ber.* **45** 3157
Cohen N 1976 *Acc. Chem. Res.* **9** 412
Danieli B, Lesma G, Palmisano G and Tollari S 1984 *J. Chem. Soc. Perkin I* 1237
Denmark S E and Germanas J P 1984 *Tetrahedron Lett.* **25** 1231
Desmaële D, Ficini J, Guingant A and Touzin A M 1983 *Tetrahedron Lett.* **24** 3083
Faulkner D J and Peterson M R 1969 *Tetrahedron Lett.* 3243
Felix D, Gschwent-Steen K, Wick A E and Eschenmoser A 1969 *Helv. Chim. Acta* **52** 1030
Fischer H and Baer E 1934 *Helv. Chim. Acta* **17** 622
Freudenberg K 1966 *Adv. Carbohydr. Chem.* **21** 1
Fucini J, Guingant A and d' Angelo J 1979 *J. Am. Chem. Soc.* **101** 1318
Fukuzaki K, Nakamura E and Kuwajima I 1984 *Tetrahedron Lett.* **25** 3591
Funk R L, Vollhardt K P C 1980 *Chem. Soc. Rev.* **9** 41
Gammil R B, Wilson C A and Bryson T A 1975 *Synth. Commun.* **5** 245
Gawley R 1976 *Synthesis* 777

Gilbert B, Autonaccio L D and Djerrasi C 1962 *J. Org. Chem.* **27** 4702
Grieco P A 1975 *Synthesis* 67
Grieco P A, Takigawa T and Moore D R 1979 *J. Am. Chem. Soc.* **101** 4380
Grieco P A, Williams E and Kanai K 1981 *Organic synthesis: Today and tomorrow* (eds) B M Trost and C R Hutchinson (New York: Pergamon Press) p. 187
Grieco P A, Williams E, Tanaka H and Gilman S 1980 *J. Org. Chem.* **45** 3539
Hanessian S 1979 *Acc. Chem. Res.* **12**
Hansen H J and Schmid H 1974 *Tetrahedron* **30** 1959
Hansen H J and Schmid H 1975 *Helv. Chim. Acta* **58** 1293
Hill R K and Gilman N W 1967 *Tetrahedron Lett.* 1421
Hill R K and Gilman N W 1967 *J. Chem. Soc., Chem. Commun.* 619
Hutchinson J H, Money T and Piper S E 1984 *J. Chem. Soc., Chem. Commun.* 455
Ireland R E and Mueller R H 1972 *J. Am. Chem. Soc.* **94** 5898
Ireland R E, Mueller R H and Willard A K 1976 *J. Am. Chem. Soc.* **98** 2868
Ireland R E, Thaisrivongs S, Vanier N and Wilcox C S 1980 *J. Org. Chem.* **45** 48
Ireland R E, Thaisrivongs S and Wilcox C S 1980 *J. Am. Chem. Soc.* **102** 1155
Johns R S, Lamberton J A and Occolowitz J L 1967 *Aust. J. Chem.* **20** 1463
Johnson W S 1976 *Angew. Chem., Int. Ed. Engl.* **15** 9
Johnson W S, Werthemann L, Bartlett W R, Brocksom J J, Lee T, Faulkner D J and Peterson M R 1970 *J. Am. Chem. Soc.* **92** 741
Jung M E 1976 *Tetrahedron* **32** 3
Jung M E and Halweg K M 1981 *Tetrahedron Lett.* **22** 3929
Jung M E and Shaw T J 1980 *J. Am. Chem. Soc.* **102** 6304
Kametani T 1979 *Pure Appl. Chem.* **51** 747
Kametani T, Kanaya N, Hino H, Hung S-P and Ihara M 1980 *Heterocycles* **14** 1771
Kametani T, Suzuki K and Nemoto H 1982 *J. Org. Chem.* **47** 2331
Kametani T, Suzuki T, Sato E, Kamada S, Tada H and Unno K 1986 *J. Chem. Soc., Perkin Trans. I*, 387
Kametani T, Suzuki T, Sato E, Nishimura M and Unno K 1982a *J. Chem. Soc., Chem. Commun.* 123
Kametani T, Suzuki T, Sato E, Nishimura M and Unno K 1982b *J. Chem. Soc., Chem. Commun.* 1201
Kimel W and Cope A C 1943 *J. Am. Chem. Soc.* **65** 1992
Kimura T and Ban Y 1969 *Chem. Pharm. Bull.* **17** 296
Koreeda M, Tanaka Y and Schwartz A 1980 *J. Org. Chem.* **45** 1173
Kupchan S M, Gaicobbe T J, Krull I S, Thomas A M, Eakin M A and Fessler D C 1970 *J. Org. Chem.* **35** 3539
Kupchan S M, Hemingway R J, Werner D, Karim A, Mcphail A T and Sim G A 1968 *J. Am. Chem. Soc.* **90** 3596
Lee K H, Wu Y S and Hall I H 1977 *J. Med. Chem.* **20** 911
Loew P and Arigoni D 1968 *Chem. Commun.* 137
Lythgoe B, Roberts D A and Waterhouse I 1977 *J. Chem. Soc. Perkin Trans. I* 2608
Marbet R and Saucy G 1967 *Helv. Chim. Acta* **50** 1158, 2091, 2095
Martinz G R, Grieco P A, Williams E, Kanai K and Srinivasan C V 1982 *J. Am. Chem. Soc.* **104** 1436
Mason H L, Myers C S and Kendal E C 1936a *J. Biol. Chem.* **114** 613
Mason H L, Myers C S and Kendal E C 1936b *J. Biol. Chem.* **116** 267
Mori K, Oda M and Matsui M 1976 *Tetrahedron Lett.* 3173
Mori K, Takigawa T and Matsuo T 1979 *Tetrahedron* **35** 933
Nakai T, Mikami K and Sayo N 1983 *J. Synth. Org. Chem. (Jpn.)* **41** 100
Nemoto H, Nagai M, Abe Y, Fukumoto K and Kametani T 1985 *J. Chem. Soc., Chem. Commun.* 1316
Newaz S S 1977 *Aldrichmica Acta* **10** 64
Nicolaou K C, Zipkin R and Tanner D 1984 *J. Chem. Soc., Chem. Commun.* 349
Ohrui Y 1981 *J. Synth. Org. Chem. (Jpn.)* **39** 275
Oppolzer W 1978 *Synthesis* 793
Piatak D M and Wicha J 1978 *J. Chem. Rev.* **78** 199
Pfiffner J J, Wintersteiner O and Vars H M 1935 *J. Biol. Chem.* **111** 585
Redpath J and Zeelen F J 1983 *Chem. Soc. Rev.* **12** 75
Reichstein T 1936 *Helv. Chim. Acta* **19** 29, 402, 979, 1107
Reichstein T 1937 *Helv. Chim. Acta* **20** 953, 978

Reichstein T and Fuw J K 1938 *Helv. Chim. Acta* **21** 1197
Rokach J, Young R N and Kakushima M 1981 *Tetrahedron Lett.* **22** 979
Sarett L H 1946 *J. Biol. Chem.* **162** 60
Sawa Y K and Matsumura H 1969 *Tetrahedron* **25** 5319
Shono T and Matsumura Y 1981 *J. Synth. Org. Chem. (Jpn.)* **39** 358
Snider B B and Kirk T C 1983 *J. Am. Chem. Soc.* **105** 2364
Steiger M and Reichstein T 1938 *Helv. Chim. Acta* **20** 817, 1040, 1164
Stevens R V and Gaeta F C A 1977 *J. Am. Chem. Soc.* **99** 6105
Stork G, Clark G and Shiner C S 1981 *J. Am. Chem. Soc* **103** 4948
Stork G, Clark G and Weller T 1984 *Tetrahedron Lett.* **25** 5367
Stork G and Kahne D E 1983 *J. Am. Chem. Soc.* **105** 1072
Stork G and Logusch W E 1980 *J. Am. Chem. Soc.* **102** 1219
Stork G and Raucher S 1976 *J. Am. Chem. Soc.* **98** 1583
Stork G and Sherman D H 1982 *J. Am. Chem. Soc.* **104** 3767
Stork G, Shiner C S and Winkler J D 1982 *J. Am. Chem. Soc.* **104** 310
Stork G and Takahashi T 1977 *J. Am. Chem. Soc.* **99** 1275
Stork G and Takahashi T 1978 *J. Am. Chem. Soc.* **99** 1275
Stork G, Takahashi T, Kawamoto I and Suzuki T 1978 *J. Am. Chem. Soc.* **100** 8272
Stork G , Winkler J D and Saccomano N A 1983 *Tetrahedron Lett.* **24** 465
Sucrow W, Caldeira P P and Slopianka M 1973 *Chem. Ber.* **106** 2236
Sucrow W and Girgensohn B 1970 *Chem. Ber.* **103** 750
Sugiyama T and Yamashita K 1980 *Agric. Biol. Chem.* **44** 1983
Sutherland J K 1980 *Chem. Soc. Rev.* **9** 265
Suzuki T, Sato E, Unno K and Kametani T 1985 *Heterocycles* **23** 839
Suzuki T, Sato E, Unno K and Kametani T 1986a *Chem. Pharm. Bull.* **34** 1584
Suzuki T, Sato E, Unno K and Kametani T 1986b *Chem. Pharm. Bull.* **34** 3135
Suzuki T, Sato E, Unno K and Kametani T 1986c *J. Chem. Soc., Perkin Trans. I* 2263
Takahashi T Okumoto H and Tsuji J 1984 *Tetrahedron Lett.* **25** 1925
Takahashi T, and Tsuji J 1982 *Kagaku* **37** 480
Takahashi T, Yamada H and Tsuji J 1981 *J. Am. Chem. Soc.* **103** 5259
Takahashi T, Yamada H and Tsuji J 1982 *Tetrahedron Lett.* 233
Takano S, Goto E, Hirama M and Ogasawara K 1981a *Heterocycles* **16** 381
Takano S, Morimoto M and Ogasawara K 1984 *J. Chem. Soc., Chem. Commun.* 82
Takano S, Numata H and Ogasawara K 1982 *Heterocycles* **19** 237
Takano S, Shibuya K, Takahashi M, Hatakeyama S and Ogasawara K 1981b *Heterocycles* **16** 1125
Takano S, Takahashi M and Ogasawara K 1980a *J. Am. Chem. Soc.* **102** 4282
Takano S, Tamura N and Ogasawara K 1981c *J. Chem. Soc., Chem. Commun.* 1155
Takano S, Yonaga M, Chiba K and Ogasawara K 1980b *Tetrahedron Lett.* **21** 3697
Takano S, Yonaga M and Ogasawara K 1981d *J. Chem. Soc., Chem. Commun.* 1153
Takigawa T, Mori K and Matsui M 1976 *Tetrahedron Lett.* 3955
Tanabe M and Hayashi M 1980 *J. Am. Chem. Soc.* **102** 862
Trost B M, Bernstein P R and Funfschilling P C 1979 *J. Am. Chem. Soc.* **101** 4378
Vamvacas C Philpsborn W V, Schlittler E, Schmid H and Karrer P 1957 *Helv. Chim. Acta* **40** 1793
Van Tamelen E E 1986 *Acc. Chem. Res* **1** 111
von E Doering W and Roth W R 1962 *Tetrahedron* **18** 69
Vittorelli P, Hansen H J and Schmid H 1975 *Helv. Chim. Acta* **58** 1293
Wenkert E, Sprague P W and Webb R L 1973 *J. Org. Chem.* **38** 4305
Wilson S R and Haque M S 1982 *J. Org. Chem.* **47** 5411
Wilson S R and Haque M S 1984 *Tetrahedron Lett.* **25** 3147
Wintersteiner O and Pfiffner J J 1935 *J. Biol. Chem.* **116** 291
Wintersteiner O and Pfiffner J J 1936 *J. Biol. Chem.* **111** 599
Ziegler F E 1977 *Acc. Chem. Res.* **10** 227
Ziegler F E and Lim H 1984 *J. Org. Chem.* **49** 3278
Ziegler F E and Sweeny J G 1969 *Tetrahedron Lett.* 1097