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Perspective

Chemistry and biology of trehazolins☆

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Abstract

Trehazolin (**1**) is a unique natural pseudodisaccharide possessing strong trehalase-specific inhibitory activity. To determine its argued correct stereochemistry, the syntheses of trehazolin (**1**), its components, the aglycon moiety, trehalamine (**4**) and its aminocyclitol hexaacetate (**6**), were accomplished from D-glucose using intramolecular [3 + 2] cycloaddition as the key step. In order to investigate the structure–activity relationships with regard to the stereochemistry of the aminocyclitol moiety and that of the anomeric position of trehazolin (**1**), trehalostatin (**2**) (trehazolin C-5 epimer), trehazolin β-anomer (**32**) and, trehazolin C-6 epimer (**33**) were all synthesized. In particular, with respect to the synthesis of trehazolin C-6 epimer (**33**), a tandem aldol–Wittig type reaction was developed as the key step to synthesize the highly functionalized 5-membered cyclitol. Moreover, on the basis of the outcome of these synthetic studies, a number of trehazolin-related compounds (**49–52**), modified at the terminal amino group of trehalamine (**4**), were synthesized to be evaluated as candidates directed to anti-NIDDM (non-insulin-dependent diabetes mellitus) drugs.

1. Introduction

The role of oligosaccharides, glycolipids, glycoproteins, and glycoconjugates in the control of living systems, and particularly in recognition between cells and in signal transdaction, is well known. Glycosyltransferases and glycosidases, primarily, manipulate the activities of glycoconjugates in these processes. In view of this, exploration and evaluation of glycosidase inhibitors play a pivotal role: glycosidase inhibitors are expected to be not only useful tools to investigate living systems controlled by glycoconjugates, but also to be potential clinical drugs against diseases caused by the failure of the glycoconjugates to perform their functions. A number of natural glycosidase inhibitors, e.g., acarbose and voglibose, have been identified and are currently being developed as potential clinical drugs. Here, we report on the chemical and biological characteristics of a novel trehalase inhibitor, trehazolin (**1**), and the determination of its characteristics.

In 1991, Ando et al. reported the isolation of trehazolin (**1**) from the culture broth of *Micromonospora* sp. strain SANK 62390. This compound is a unique natural pseudodisaccharide showing a strong trehalase-specific inhibitory activity [1]. Almost concurrently, the isolation of a compound named trehalostatin (**2**) from the culture broth of *Amicoratopsis*

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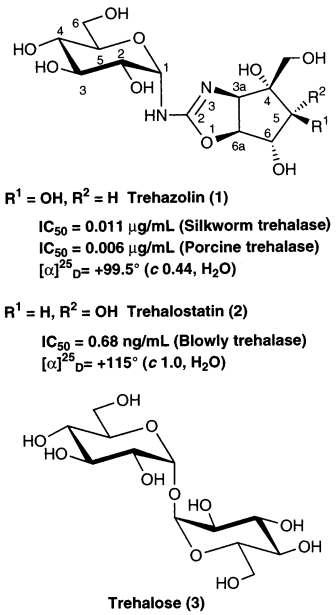


Fig. 1. Structures of trehazolin (**1**), trehalostatin (**2**), and trehalose (**3**).

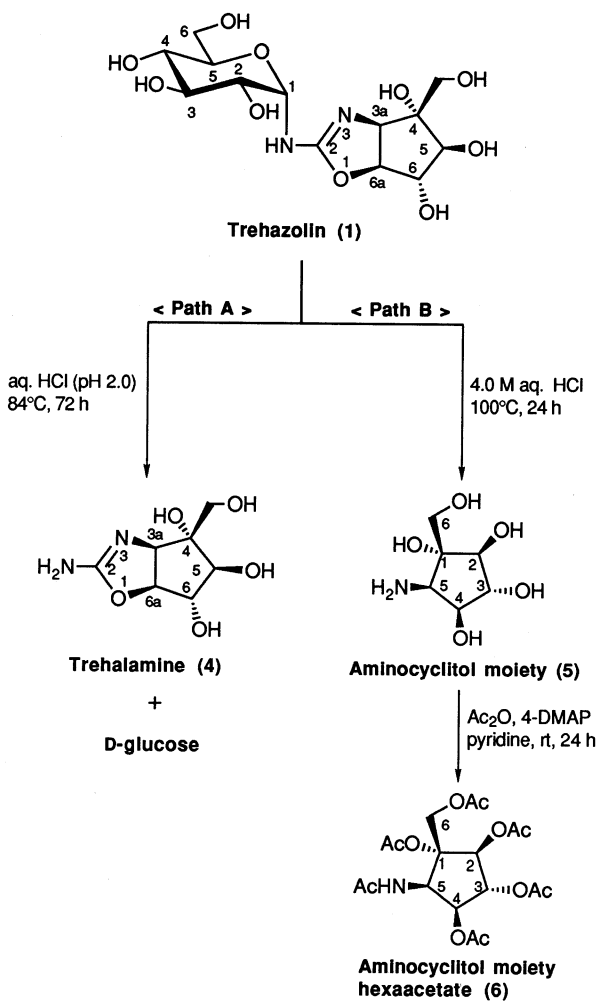


Fig. 2. Degradation studies of trehazolin (**1**).

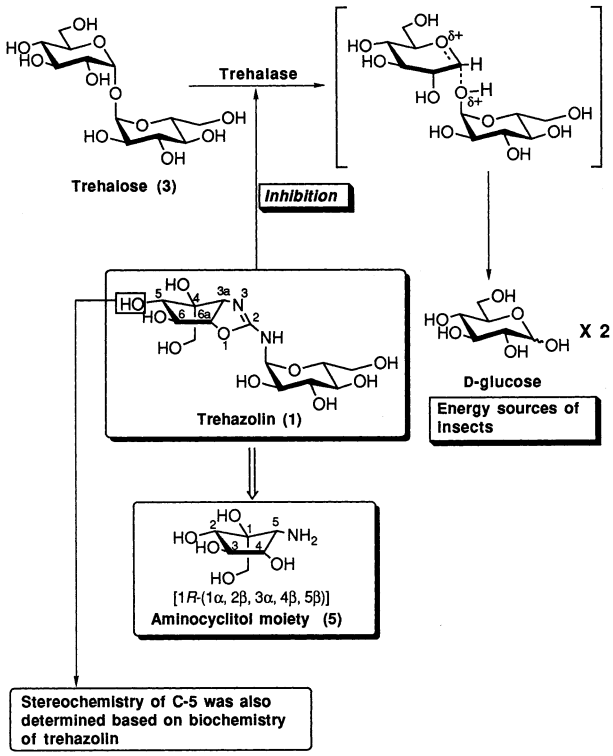


Fig. 3. Trehazolin (**1**): potentially a new type of insecticide.

trehalostatica was also reported [2]. Trehalostatin (**2**) was reported as the epimer of the C-5 position of the aglycon of trehazolin (**1**). According to the reported physical and biological data, trehalostatin (**2**) seemed to be identical to trehazolin (**1**) (Fig. 1). Because both compounds are noncrystalline, X-ray microanalysis could not be used to determine the correct stereochemistry; hence, the stereochemistry regarding the C-5 position of the aglycons remained unknown.

Therefore, we attempted a series of degradation studies of trehazolin (**1**) to try to obtain degradation products from which the correct stereochemistry could be determined (Fig. 2). Hydrochloric acid degradation provided two degradation products: the aglycon moiety trehalamine (**4**) and the aminocyclitol moiety **5**, from which we next obtained the acetylated product **6**. However, all products were noncrystalline. Consequently, they could not be used to determine the correct stereochemistry.

Fig. 3 shows the predicted inhibition mechanism of trehazolin (**1**). It is considered that

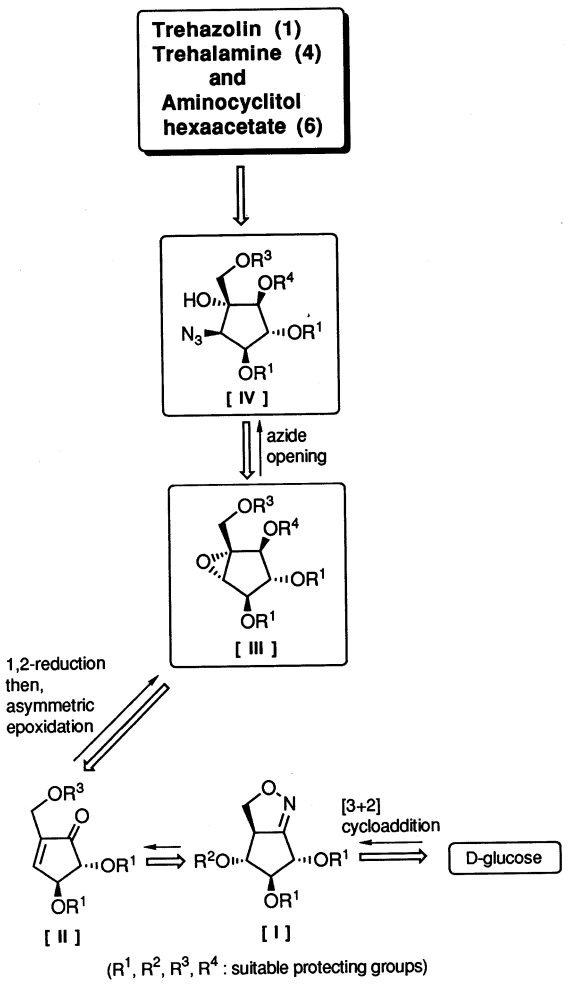


Fig. 4. Retrosynthetic analysis of the aminocyclitol moiety.

D-glucose, which is a product of degradation of trehalose (**3**) with trehalase, is eventually used as an energy source by insects, and trehazolin (**1**), which inhibits the enzyme, would thus be expected to be a new type of potential insecticide. Our group has also considered the correct absolute stereochemistry of trehazolin (**1**) on the basis of this inhibition mechanism in addition to the NMR data. It was surmised that the actual structural resemblance between trehazolin (**1**) and trehalose (**3**) may have a bearing on the generation of the activity of trehazolin towards various trehalases, and we hypothesize the absolute configuration of its aminocyclitol moiety as [1*R*-(1α,2β,3α,4β,5β)].

Then, in order to verify the proposed correct structure of trehazolin (**1**), a series of synthetic studies were performed. The objectives of the synthetic studies were (a) to determine the absolute configuration, including the correct stereochemistry of trehazolin (**1**), (b) to investigate the relationship between the stereochemistry of trehazolin (**1**) and its specific enzyme inhibitory activity, and (c) to identify the chemical reaction pathway leading to related compounds modified at the amino group of the aglycon moiety of trehazolin (**1**) and to investigate the structure–activity relationships of these derivatives.

2. Retrosynthetic analyses of trehazolin (1), trehalamine (4) and the aminocyclitol moiety hexaacetate (6) [3]

As the gluconic unit of trehazolin (**1**) is a D-glucose and the stereocenter of its aglycon unit is equivalent to that of D-glucose, D-glucose was chosen as the starting material for the synthesis of trehazolin (**1**). The retrosynthetic analysis of trehazolin (**1**) is outlined in Fig. 4. To synthesize trehazolin (**1**) and its degradation products (**4**) and (**6**), the azide alcohol **IV** is considered to be the significant intermediate. This azide alcohol **IV** would be converted into the aminocyclitol derivative necessary to synthesize trehazolin (**1**) and its

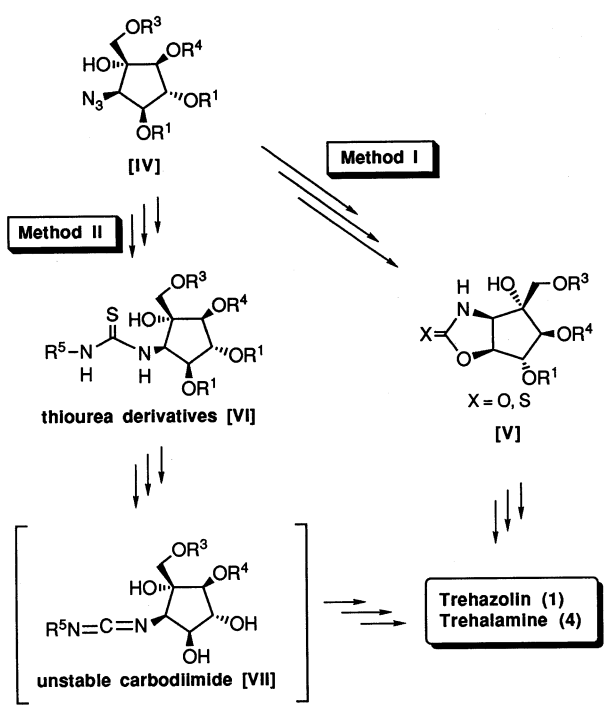
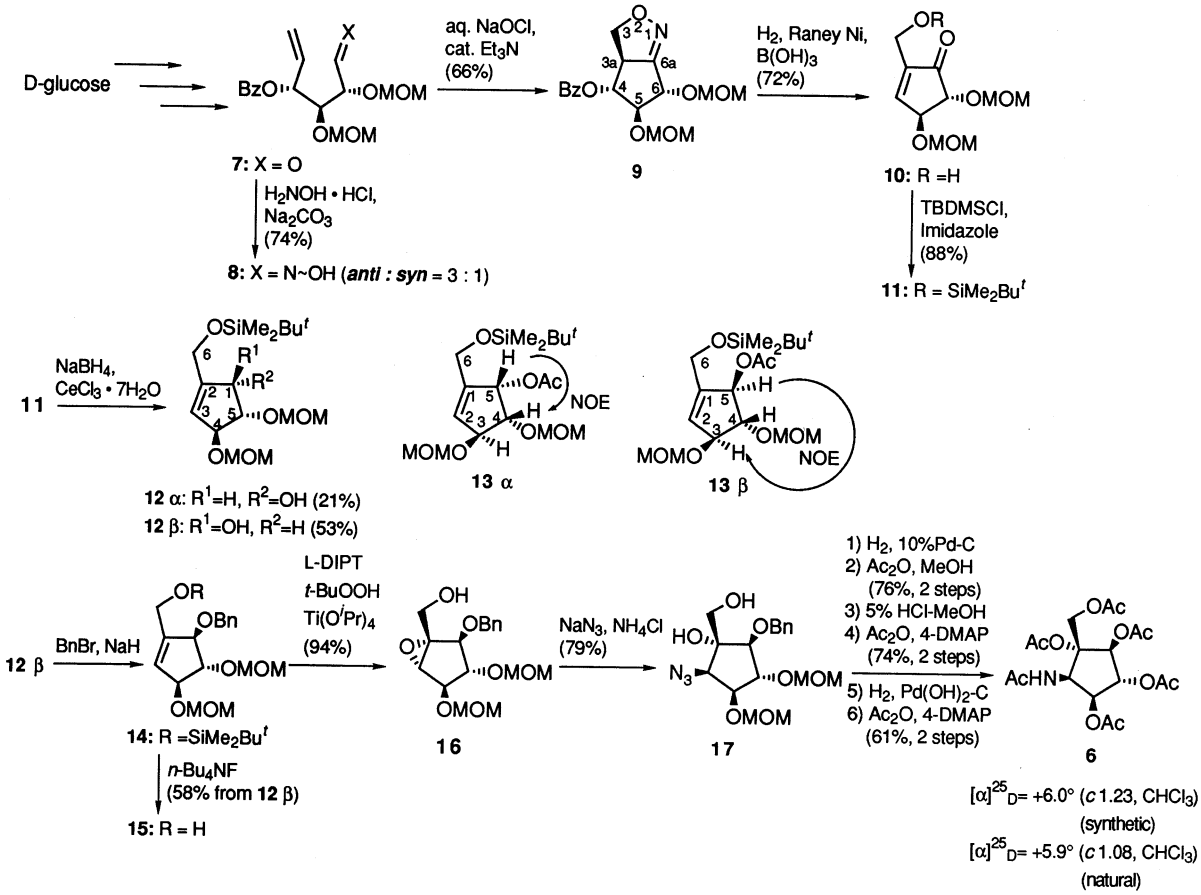


Fig. 5. Construction of the aminooxazoline framework.



Scheme 1.

components **4**, **5** and **6**, and the azide alcohol **IV** would be synthesized from the chiral epoxide **III** by regiospecific azide opening. Asymmetric epoxidation of the allyl alcohol derived from the enone **II** through a series of steps, including the 1,2-reduction of its carbonyl group, would provide the corresponding chiral epoxide **III**.

The stereochemistry of the hydroxy group induced by the 1,2-reduction of the carbonyl group of the enone **II**, is the argued one, and the synthesis of trehalostatin (**2**) would be performed from the stereoisomer obtained by this 1,2-reduction. The formation of the enone **II** from the isoxazoline derivative **I**, and the β-elimination would occur simultaneously, the latter being induced by the electron-withdrawing group R^2 to give the hydroxymethyl enone **II**. The isoxazoline derivative **I** would be derived from D-glucose via intramolecular [3 + 2] cycloaddition. There are two methods that can be employed to form the aminooxazoline ring, as illustrated in Fig. 5.

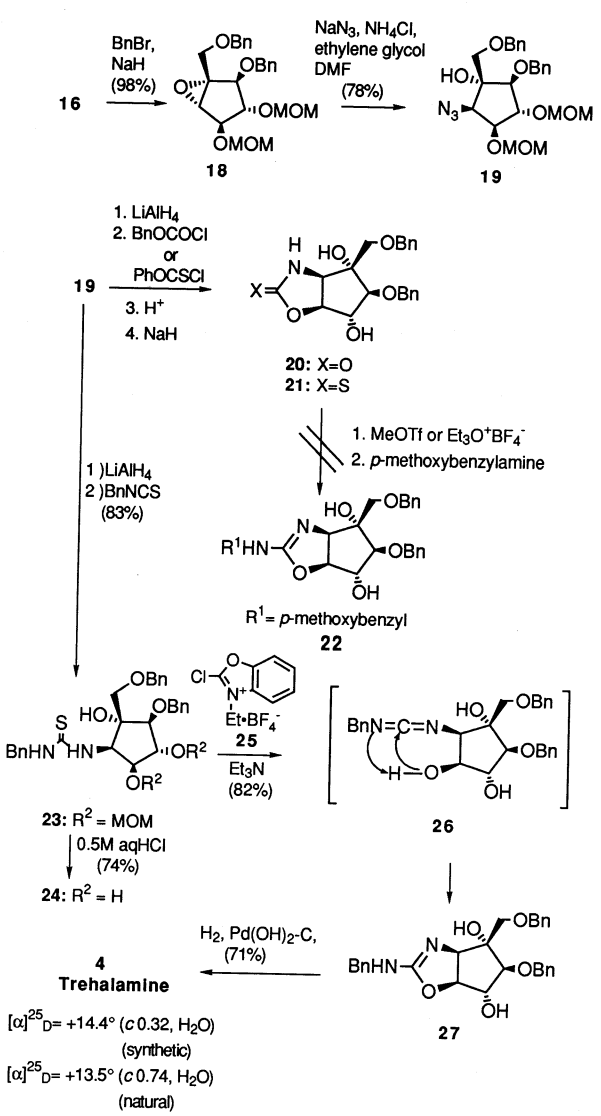
Method I is the formation of the aminooxazoline ring from the oxazolidinone derivatives **V**, a method used for Trost's allosamizoline synthesis [4].

Method II is the ring formation from thioureas **VI** via the carbodiimide alcohols **VII**, as aminooxazoline can be considered to be a carbodiimide alcohol.

As the first stage of the synthetic studies of trehazolin (**1**), the determination of the absolute configuration of the trehazolin aminocyclitol moiety **5** was accomplished by the synthesis of its hexaacetate **6**.

3. Synthesis of the aminocyclitol moiety of trehazolin as its hexaacetate (6) [3,5]

Intramolecular [3 + 2] cycloaddition of the oxime **8**, derived from D-glucose according to



Scheme 2.

the method developed by Bernet and Vasella [6], furnished the corresponding isoxazoline **9**. In general, the hydrogenolysis of isoxazloine with Raney nickel results in conversion to a hydroxymethyl ketone. However, in this case, by virtue of the electron-withdrawing effect of the benzoyl group, β-elimination of the benzoyloxy group by the generated ketone was induced, and the corresponding hydroxymethyl enone **10** was obtained.

Silylation of the enone **10**, and subsequent 1,2-reduction of the corresponding ketone **11**, afforded a separable 1:2.5 mixture of alcohols **12**.

The configurations of the C-1 positions of these alcohols **12** were determined by analysis of the ^{1}H NMR data of the acetates **13**; that is, the NOE between H-5 and H-4 of compound **13**α and that between H-5 and H-3 of compound **13**β were observed.

Benzylation of the alcohol **12**β, possessing the desired configuration, and subsequent removal of the TBDMS group afforded the corresponding allyl alcohol **15**. Several types of epoxidation towards the allyl alcohol **15** were attempted; Sharpless' epoxidation using diisopropyl L-tartrate furnished the desired epoxide **16** as a single isomer.

Finally, the synthesis of the aminocyclitol moiety as its hexaacetate **6** was accomplished by the regiospecific azide opening to chiral epoxide **16**, deprotection, and subsequent complete acetylation.

This synthetic hexaacetate was identical in all respects to the hexaacetate of the degradation product, aminocyclitol, and the absolute configuration was found to be [1*R*-(1α,2β,3α,4β,5β)] as expected (Scheme 1).

4. Syntheses of trehalamine (4) and trehazolin (1) [3,7]

Next, the synthesis of trehazolin aglycon, trehalamine (**4**), was tried (Scheme 2). The key aspect of this synthesis was the method by which the aminooxazoline ring was formed. First, Method I used for Trost's allosamizoline synthesis [4] was attempted. O-Alkylation of the oxazolidinone derivatives **20** and **21**, both derived from the chiral epoxide **16** via regiospecific azide opening and subsequent amination, did not yield the desired product **22**. As a result, Method II, the cyclization via the carbodiimide alcohol, was attempted. As shown in Fig. 6, the aminooxazoline ring **IX** can be considered as the equivalent to the *cis*-carbodiimide alcohol **VIII**. Then, a number of methods to generate carbodiimides were investigated, and the method of Mukaiyama, shown in Fig. 6, was selected. This is the synthetic method using 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**25**) and related reagents, which features β-elimination of intermediate **XI** derived from the thiourea **X** and the reagent **25**, furnishing the corresponding carbodiimide **XII**. This method was

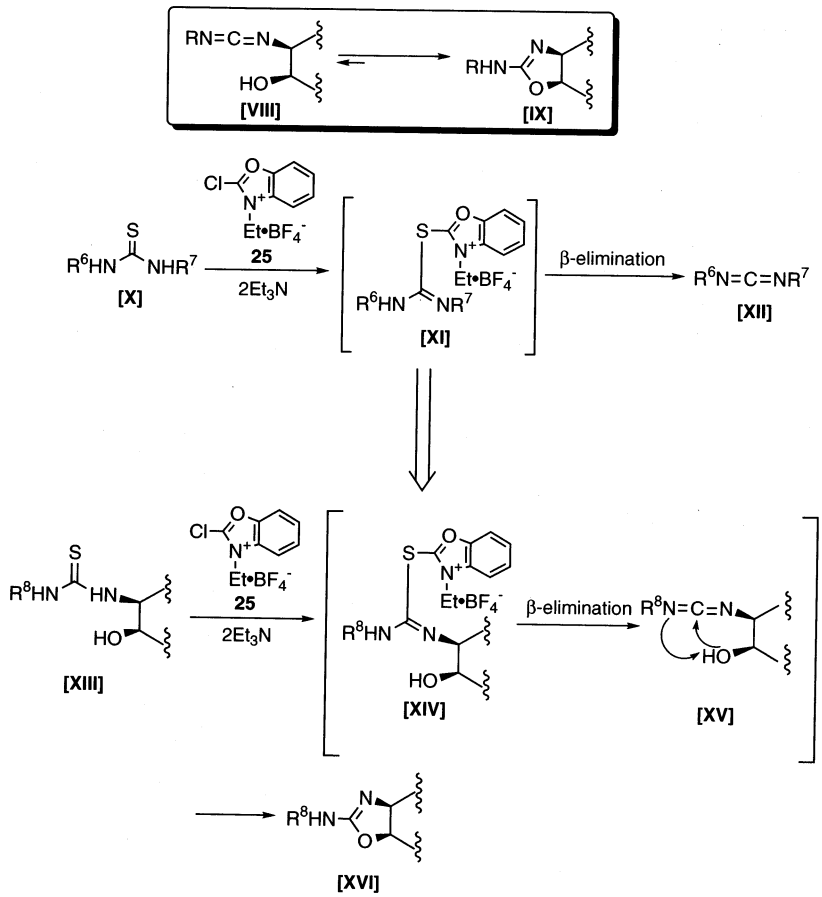


Fig. 6. Formation of an aminooxazoline ring using Mukaiyama reagents.

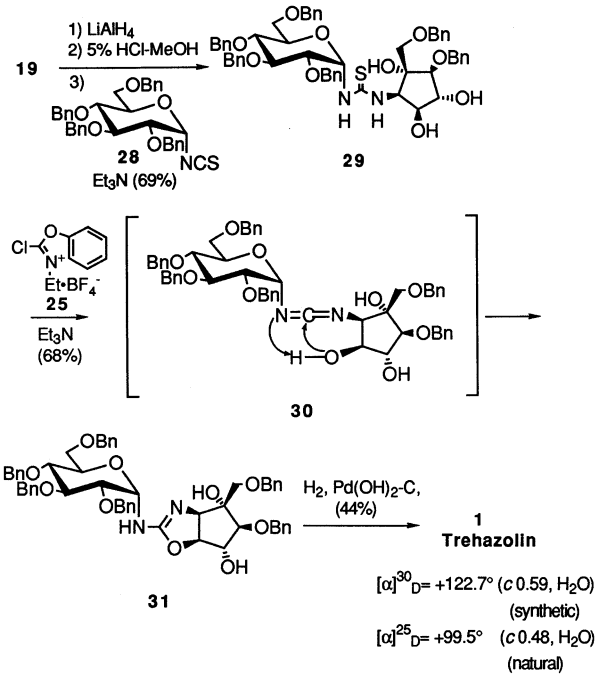
then applied to a series of *cis*-thiourea alcohols **XIII**. Consequently, cyclization of the cis-adjacent hydroxy group and the carbodiimide portion of the carbodiimide alcohol **XV** would obtain the aminooxazoline **XVI**. Then, the thiourea **24** derived from the azide alcohol **19** was treated with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**25**), furnishing the aminooxazoline derivative **27**.

Finally, the aminooxazoline **27** was hydrogenolyzed to cleave the three benzyl groups and to give trehalamine (**4**). This synthetic trehalamine was identical in all respects to natural trehalamine.

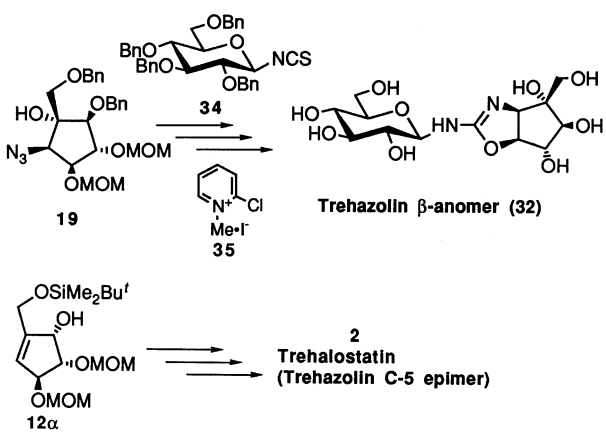
Based on the synthesis of trehalamine (**4**), the synthesis of trehazolin (**1**) was undertaken. Coupling between the amino alcohol derived from the azide compound **19**, and the α-D-glucopyranosyl isothiocyanate derivative **28**, as synthesized by Jose Camarasa [8], afforded the α-D-glucopyranosyl thiourea derivative **29**. Treatment of this thiourea **29** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**25**) furnished the aminooxazoline derivative **31**. Finally, this aminooxazoline **31** was hydrogenolyzed to cleave the benzyl groups and to generate trehazolin (**1**). This synthetic trehazolin was identical to the natural trehazolin in all respects, including biological activities (Scheme 3).

5. Synthetic studies and evaluation of trehazolin stereoisomers

The success of total synthesis of trehazolin (**1**) encouraged us to investigate the structure–activity relationships regarding the inhibitory activities towards various α-glucosidases resulting from the stereochemistry of trehazolin. To investigate the influence of the stereochemistry of the anomeric position on the inhibitory activities, trehazolin β-anomer **32** was synthesized from the azide **19** and β-D-glucopyranosyl isothiocyanate derivative **34** (Scheme 4) [9]. To avoid anomerization and



Scheme 3.



Scheme 4.

contamination of the α-anomer, 2-chloro-1-methylpyridinium iodide (**35**) was used in place of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**25**) for the ring formation.

At the step of 1,2-reduction of the hydroxymethyl enone **11**, the allyl alcohol **12**α was also obtained, and trehalostatin (**2**) (trehazolin C-5 epimer) was then synthesized from this allyl alcohol according to the synthetic route of trehazolin (**1**) (Scheme 4) [10].

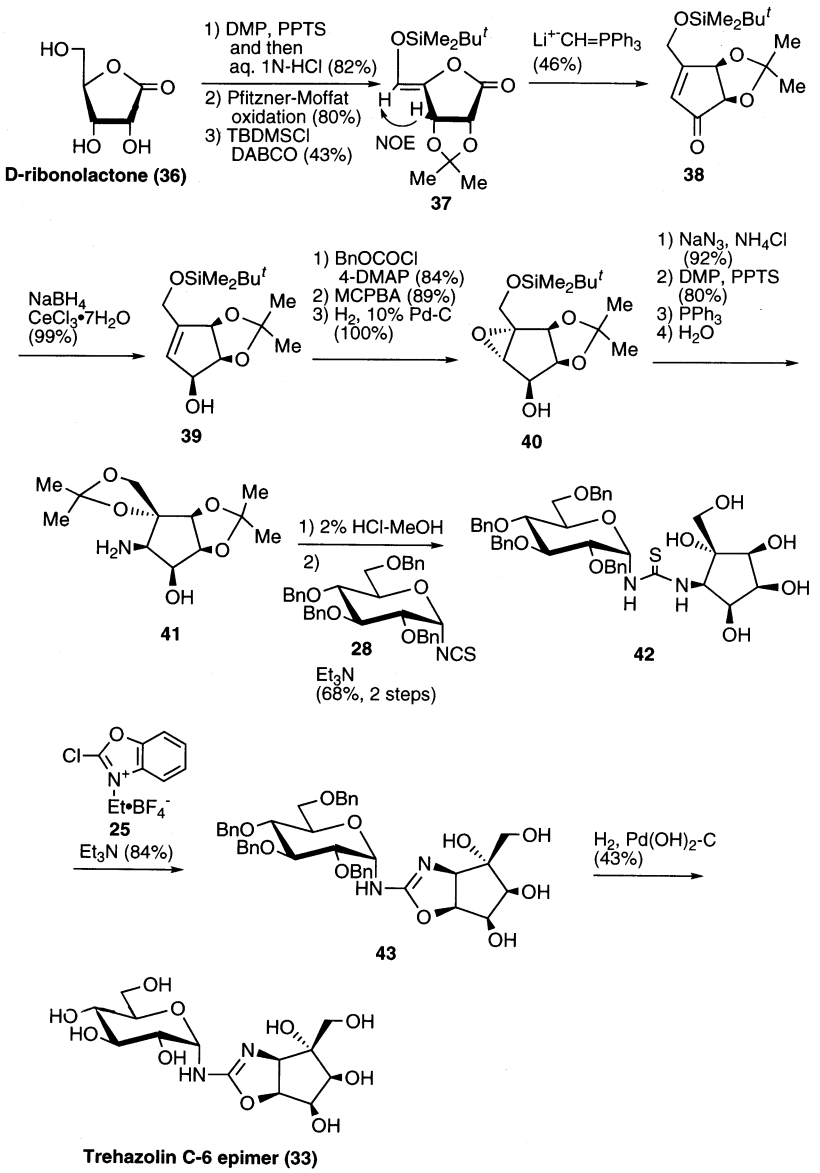
The physical data, including the ^{1}H NMR spectrum of trehalostatin (**2**), were quite close to those of trehazolin (**1**) itself, but the inhibitory activities of this compound towards trehalases were much weaker than those of trehazolin (**1**).

As a result, the argued stereochemistry of the aminocyclitol moiety of trehazolin (**1**) and trehalostatin (**2**) was determined to be [1*R*-(1α,2β,3α,4β,5β)] by these synthetic studies. Next, in order to investigate further the structure–activity relationships regarding the inhibitory activities towards various α-glucosidases resulting from the stereochemistry of the aminocyclitol moiety, trehazolin C-6 epimer **33** was synthesized (Scheme 5) [11,12]. In this synthesis, the challenging tandem aldol–Wittig type reaction was performed to construct the enone **XVII** (Fig. 7). As shown in Fig. 8, it was expected that treatment of the silylenol lactone **XVIII**, which was derived from D-ribonolactone **36**, with the α-lithiated phosphorane would give the enone **XVII** via the aldol reaction and subsequent intramolecular Wittig reaction in one pot. Scheme 5 shows the practical synthesis.

The treatment of the silylenol lactone **37**, which was derived from D-ribonolactone **36** in three steps, with the lithiated phosphorane furnished the cyclopentenone **38** in medium yield. This reaction should thus have synthetic utility for the one-step synthesis of cyclic α,β-unsaturated ketones from cyclic enol ester type derivatives.

Afterward, the synthesis proceeded basically according to trehazolin synthesis, including the 1,2-reduction of the enone **38**, stereoselective epoxidation and regiospecific azide opening of the epoxide **40**, coupling between the amine derived from compound **41** and the isothiocyanate **28** and cyclization to form the aminooxazoline ring **43**.

In this synthesis, an interesting chemical aspect of the trehazolins was found (Fig. 9): the transcyclization from the [4.3.0] bicyclo aglycon to the [3.3.0] bicyclo aglycon. Hydrogenolysis of the [4.3.0] bicyclo analogue **47** derived from the amine **45** unexpectedly gave the trehazolin C-6 epimer **33**. This compound was identical to the compound derived from the [3.3.0] bicyclo analogue **46** in all respects. Thermodynamically speaking, the [3.3.0] bicyclo ring system is expected to be more stable than the [4.3.0] bicyclo ring system. Therefore,



Scheme 5.

we conjectured that in the hydrogenolysis of compound **47**, the generated adjacent cis hydroxyl group transcyclized from the 6-membered ring to the 5-membered ring to give the more thermodynamically stable [3.3.0] bicyclo ring, trehazolin C-6 epimer **33**.

A summary of the structure–activity relationships in regard to the inhibitory activities resulting from the stereochemistry of aminocyclitol moieties of the trehazolins is given in Table 1. A comparison of trehazolin (**1**), β-anomer **32**, trehalostatin (**2**) (trehazolin C-5 epimer) and trehazolin C-6 epimer **33** showed that only trehazolin (**1**) has the strong trehalase–specific inhibitory activity. Therefore, we conclude that its configuration is nearly similar to the intact trehalose and that the configuration is essential to generate specific inhibitory activity. Furthermore, the enzyme is thought to recognize the slight differences in stereochemistry at the inhibition step.

6. Synthetic studies and evaluation of trehazolin-related compounds directed to an anti-NIDDM drug [13]

Based on the synthetic studies and chemical properties of the trehazolins, the application

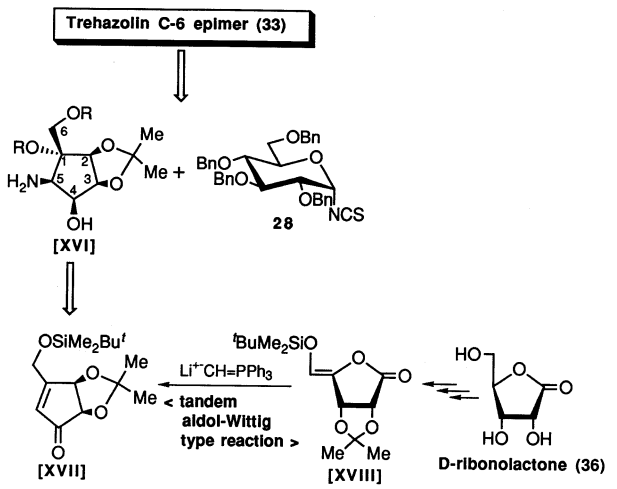


Fig. 7. Retrosynthetic analysis of a trehazolin C-6 epimer.

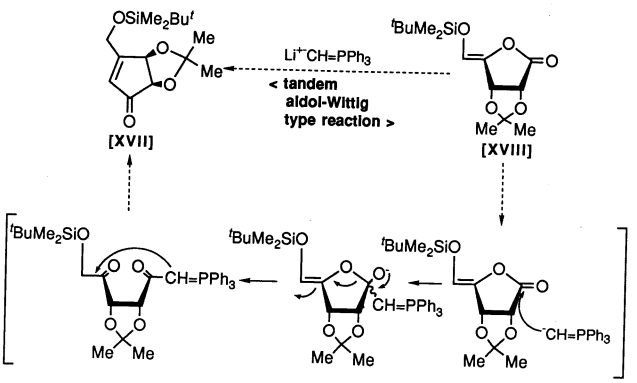


Fig. 8. Mechanism of a tandem aldol–Wittig type reaction.

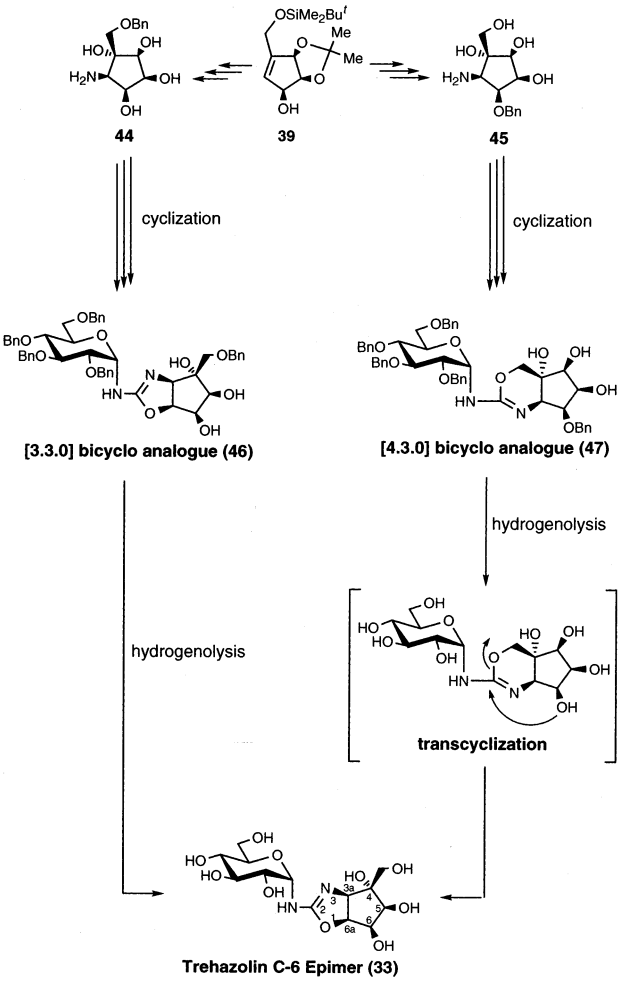


Fig. 9. Chemical properties of trehazolin C-6 epimer: transcyclization from [4.3.0] bicyclo aglycon to [3.3.0] bicyclo aglycon.

of trehazolin synthesis to potential clinical drugs was undertaken.

A simplified metabolic pathway of maltose **48**, which serves as an energy source to human life, is shown in Fig. 10. Maltose **48** is degraded by a glucosidase, maltase, and converted to D-glucose, which is used as an energy source by humans. It has been speculated that the excess D-glucose produced in this pathway possibly causes non-insulin-dependent diabetes mellitus (NIDDM). In consideration of this pathway, potential maltase inhibitor **XIX** was designed. This compound belongs to a group of maltose mimics, possessing the pseudo-D-glucose moiety, trehala-

Table 1
Inhibitory activities of trehazolin derivatives towards various α-glucosidases (IC_{50}: μg/mL)[a]

Enzyme	Origin	TRZ	TRA	AMM	**2**	**32**	**33**
Trehalase	Silkworm	0.011	37	>100	>100	0.19	>100
Trehalase	Porcine	0.006	0.08	0.25	20	0.013	0.4
Maltase	Rat	76	75	>100	>100	>100	20
Maltase	Yeast	>100	67	>100	NT	8.6	>100
Isomaltase	Rat	3.9	100	>100	15	>100	0.6
Sucrase	Rat	76	14	>100	>100	>100	29
α-Amylase	Porcine	>100	>100	>100	>100	>100	>100

[a] TRZ, trehazolin; TRA, trehalamine; AMM, aminocyclitol moiety.

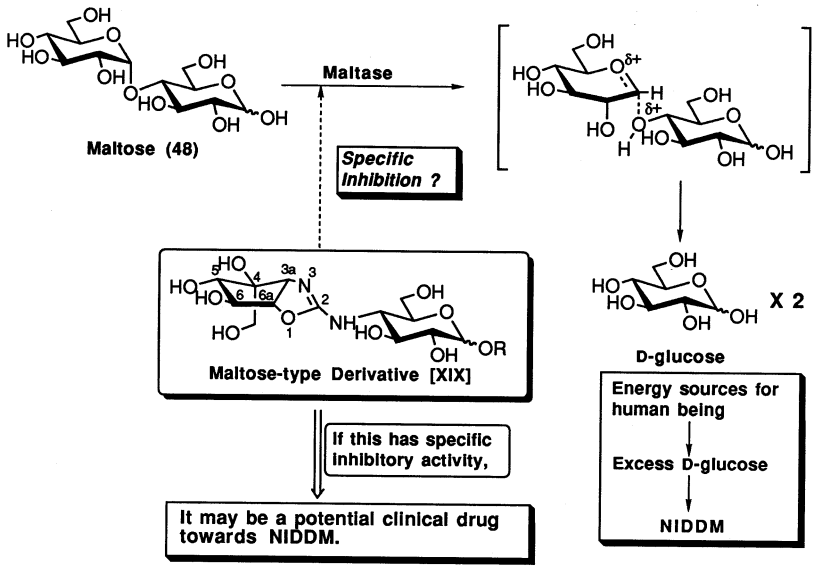


Fig. 10. Application of trehazolin to potential clinical drugs.

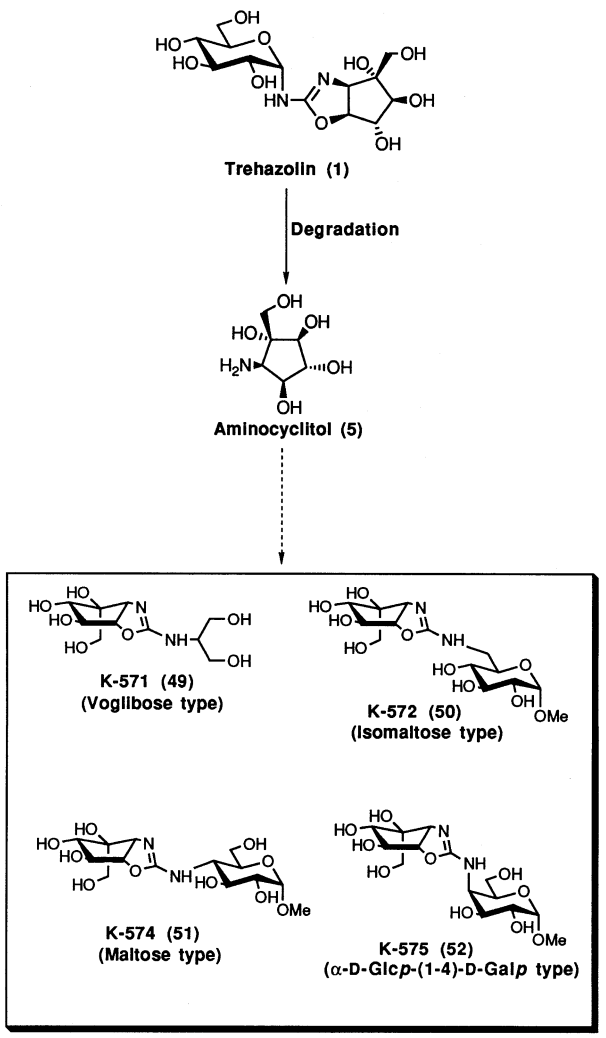


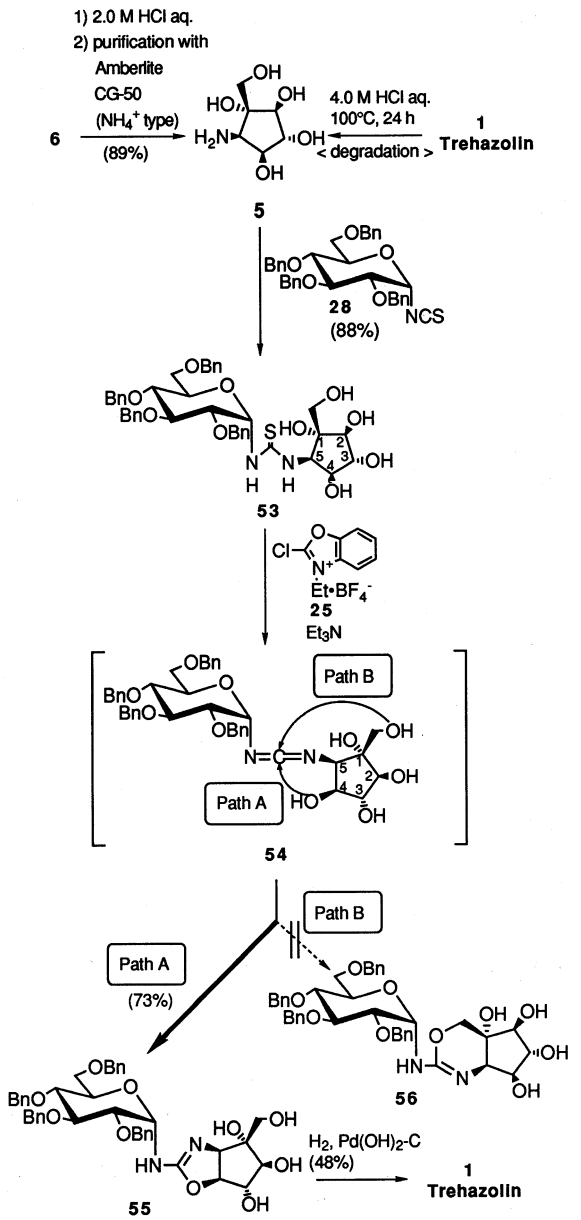
Fig. 11. Design of trehazolin derivatives modified at the terminal amino group of aglycon.

mine (**4**), and was expected to act as a potential maltase-specific inhibitor. Then, the synthesis of the compounds directed to the potential clinical drugs of NIDDM was performed.

Fig. 11 shows the trehazolin derivatives designed to be potential clinical drugs against NIDDM. K-571 (**49**) was designed from voglibose, which was derived from a natural glucosidase inhibitor, valiolamine; K-572 (**50**) and -574 (**51**) were designed as isomaltose or maltose mimics; K-575 (**52**) was designed to confirm the general application of the synthetic technique.

The point we considered next was the utility of the natural trehazolin aminocyclitol moiety **5**. As described above, the [3.3.0] bicyclo system of the aglycon is quite stable thermodynamically, and such type of ring formation proceeded exclusively with the formation of the desired product. The thermodynamic stability indicated that the non-protected aminocyclitol **5**, itself obtained as a degradation product of natural trehazolin (**1**), could be used to synthesize the compounds **49**–**52** shown in Fig. 11. Therefore, based on the chemical aspects obtained in the synthesis of trehazolin C-6 epimer **33**, the synthesis of these compounds from this non-protected aminocyclitol **5** was arranged.

As the prologue of this program, the reconstruction of trehazolin (**1**) from its degrada-



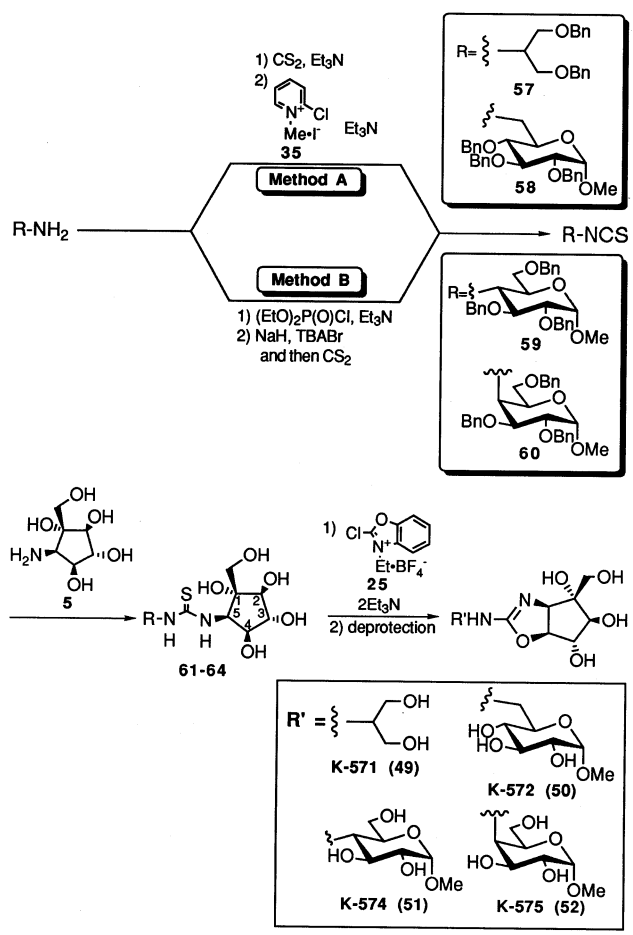
Scheme 6.

tion product, aminocyclitol **5** was tried because there were still two possibilities of cyclization (Paths A and B) after the treatment of thiourea **53** with reagent **25** in this synthesis utilizing the intact aminocyclitol **5** (Scheme 6) [3]. However, as indicated in the synthesis of trehazolin C-6 epimer (**33**), only the expected trehazolin (**1**) was synthesized from the intact aminocyclitol **5** according to the synthetic route shown in Scheme 6, and it was found that the degradation product, aminocyclitol **5**, could be used to synthesize the derivatives **49–52**.

Subsequently, the aforementioned derivatives **49–52** were synthesized [13]. The isothiocyanates **57–60** were prepared from the corresponding amines by two methods (Scheme 7). Method A was the one-pot isothiocyanation using 1-methyl-2-pyridinium iodide (**35**), and Method B was the typical Wittig–Horner–Emmons type isothiocyanation.

Coupling of the isothiocyanates **57–60** and the aminocyclitol **5**, degraded from natural trehazolin (**1**), afforded the corresponding thioureas **61–64**, which were further converted to the desired aminooxazolines **49–52**.

Inhibitory activities of the derivatives towards various glucosidases are shown in Table 2. Surprisingly, K-572 (**50**) inhibited maltase and sucrase more potently than did trehazolin. Also surprisingly, K-574 (**51**), the maltose mimic, did not show inhibitory activity at all, and K-571 (**49**) lacked the specificity of inhibition, in spite of the weak activities towards all



Scheme 7.

Table 2
Inhibitory activities of pseudodisaccharides possessing trehalamine moiety (IC_{50}: μg/mL)[a]

Enzyme	Origin	TRZ	**49**	**50**	**51**	**52**
Trehalase	Silkworm	0.011	69	>100	>100	>100
Trehalase	Porcine	0.006	56	92	>100	30
Maltase	Rat	76	35	9	>100	>100
Maltase	Yeast	>100	NT	11	NT	NT
Isomaltase	Rat	3.9	>100	55	>100	72
Sucrase	Rat	76	31	10	>100	>100
α-Amylase	Porcine	>100	NT	NT	>100	>100

[a] TRZ, trehazolin.

α-glucosidases listed here. In this case, it is possible that the relationship between inhibitory activity generation and the structural resemblances of the inhibitor to the substrates was not always present, unlike trehazolin. And for the design of the corresponding analogues, further studies, including the accurate structural analyses for the complexes consisting of the inhibitors and target enzymes, are necessary.

7. Conclusions

From our synthetic studies, we can conclude that (a) the total synthesis of trehazolin (**1**) can be accomplished from D-glucose by using [3 + 2] cycloaddition as the key step, and the argued absolute configuration of its aminocyclitol moiety **5** was determined as [1*R*-(1α,2β,3α,4β,5β)]; (b) the synthetic method for the 5-membered cyclitol using the tandem aldol–Wittig type reaction was successfully applied to the synthesis of trehazolin C-6 epimer **33**; and (c) the formation of the aminooxazoline ring using 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**25**) is applicable to the ring formation of the terminal amino group of the trehazolin aglycon, trehalamine (**4**). With regard to the structure–activity relationship of the trehazolins, we found that (a) the stereochemistry of the trehazolins influences their inhibitory activity towards trehalases; the stereochemistry is similar to that of the intact trehalose and is essential in order to generate this compound's inhibitory activity and (b) the trehazolin-related compounds **49–52** unexpectedly did not possess the strong maltase- or isomaltase-specific inhibitory activities required of potential clinical drugs against NIDDM.

Recently, a variety of the reports regarding synthetic studies of the trehazolins have been presented due to the chemical and biological interests to the trehazolins, as described in Refs. [14–31]. For instance, Ogawa et al. synthesized trehazolin and its related compounds from *myo*-inositol, and they also contributed to the studies of the structure–activity relationship of the trehazolins [14–22]. Ganem et al. synthesized trehazolin C-6 epimer independently, and their synthetic studies of trehazolin itself are also proceeding [26,29]. On the other hand, Knapp et al. reported the synthesis of maltose type of trehazolin derivative from D-ribonolactone to elucidate the potency of trehalamine as a pseudo-D-glucose [24]. This means that the circumstances surrounding trehazolin are very dynamic, and it is expected that research on the trehazolins will be further developed, and a more interesting outcome of these studies will be forthcoming.

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