rule can only be used to compare unbranched PAHs having the same number of rings but different arrangements of kinks or different numbers of rings with the same arrangements of kinks. In effect, it allows for a limited refinement in our $\alpha' > \alpha > \beta$ rule: **39** and **40** are both α cases, and we are now able to predict that **39** is the more stable.

Concluding Remarks

Simple rules allow one to prescreen certain kinds of PAH and related molecules for likelihood and/or degree of tumorigenic activity. The rules are based on an emerging picture of the chemical process by which certain PAHs lead to the induction of tumorogenesis and are supported by quantum chemical calculations as well. Because of our incomplete understanding of the reactions involved in this chemical process, predictions of relative tumorogenicity/carcinogenicity will sometimes be wrong, even when they are correct about the relative stabilities of ions. Despite this risk, the approach outlined here is useful since it requires little effort, often gives correct predictions, and, when it does not, provides a clue that the tumorogenic activity of the molecule in question is not controlled by the energy of formation of the triol–carbocation from the diol–epoxide.

An Introduction of Chiral Centers into Acyclic Systems Based on Stereoselective Ketone Reduction

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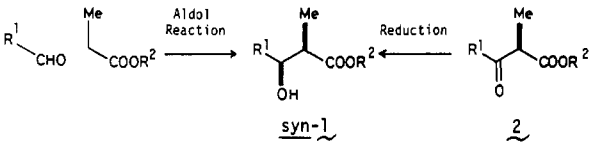
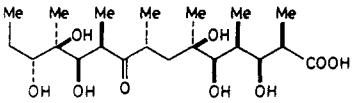
In connection with synthetic studies of polyoxomacrolide antibiotics, stereocontrolled reactions in acyclic systems have been extensively investigated. Among them, the stereoselective synthesis of *syn*-α-methyl-β-hydroxy esters **1** has attracted the attention of many synthetic organic chemists, since these moieties repeatedly appear in the framework of the above antibiotics (for example, erythronolide A seco acid, see Scheme I). Moreover, these moieties are an important building block for the synthesis of a complex array of methyl and hydroxyl functions involved in these natural products. Efforts have been focused mainly on the development of the regio- and stereocontrolled aldol reaction, and excellent results have been accumulated.[1] Alternatively, we undertook to synthesize the desired syn compounds **1** by a route based on their biogenesis, namely, by a stereoselective reduction of the corresponding α-methyl-β-keto esters **2**.

The polyoxomacrolide and polyether antibiotics are biogenetically classified as polyketides, and their carbon skeletons are believed to be constructed by a series of condensation of enzyme-bound acetate, propionate, or butyrate with the corresponding malonates. Quite recently, it was firmly established by two groups[2,3] that

Scheme I
Synthetic Routes for *syn*-α-Methyl-β-hydroxy Esters





Erythronolide A seco-acid

the oxygen atoms of the first-formed macrolide or polyether aglycons originated from precursor propionates. These findings strongly suggest that the absolute configurations of most of the hydroxyl groups should be set up by direct enzymatic reduction of the corresponding β-keto esters or poly-β-ketone intermediates.

Our primary approach began with an effort to design a chemical process corresponding to the enzymatic reduction of α-alkyl-β-keto esters in the hope of constructing multichiral centers involving hydroxyl groups.

Reduction of α-Methyl-β-Keto Esters (Type 1 Reduction) and α-Methyl-β-Hydroxy Ketones (Type 2 Reduction) with $Zn(BH_4)_2$

Our working Yamaguchi[9a] for the formation of *syn*-**1** was that if two oxygen functions in α-methyl-β-keto esters **2** are arranged to come to the same plane by coordination with a complex metal hydride reagent, hydride anion should attack the carbonyl carbon from

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Tadashi Nakata was born in Japan in 1943, received his B.S. and M.S. degrees from Hokkaido University, and then joined RIKEN, where he worked with the late Dr. Akira Tahara. He received his Ph.D from Hokkaido University in 1974 and spent 2 years at Harvard University with Prof. Yoshito Kishi as a postdoctoral fellow. Since then, he has been engaged in the synthesis of polyoxomacrolide and ionophore antibiotics.

(1) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. Evans, D. A. *Ibid.* **1982**, *15*, 23. Heatcock, C. H. In "Current Trends in Organic Synthesis"; Nozaki, H. Ed.; Pergamon Press: Oxford, U.K., 1983; p 27.
(2) Cane, D. E.; Taylor, P. B.; Liang, T-C. *Tetrahedron* **1983**, *39*, 3449.
(3) Hutchinson, C. R. *Acc. Chem. Res.* **1983**, *16*, 7.

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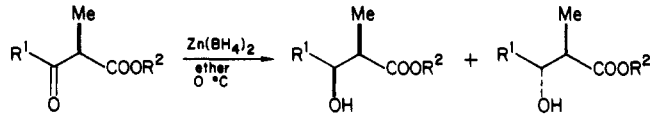
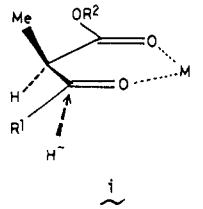
Table I
Reduction of β-Keto Esters 2 with $Zn(BH_4)_2$ (Type 1 Reduction)



entry	R^1	R^2	*syn*-1/*anti*-3	% yield
1	Ph	Me	>99/<1	98
2	CH_2=C(Me)	CH_2Ph	>99/<1	80
3	$MeCH_2CH$=C(Me)	CH_2Ph	>99/<1	85
4	PhCH=CH	Me	10/1	79
5	$PhCH_2CH_2$	Me	3/1	98
6	Me	CH_2Ph	2/1	95

the opposite side of the α-methyl group producing the desired syn compound 1 (see i). Canceill et al.[4] have



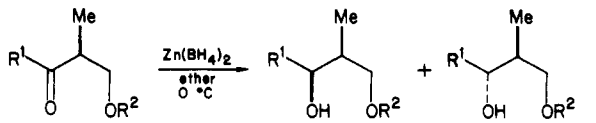
i

already reported that $LiAlH_4$ reduction of 2-benzoylpropionate **2** (R^1 = Ph, R^2 = Me) affords syn glycol **5** (R^1 = Ph, R^2 = H) predominantly (syn/anti ratio, 90/10), while the reduction with KBH_4 produces anti isomer **6** as a main product (syn/anti ratio, 27/73). We considered that this different selectivity could be explained by assuming that a contribution of a cyclic transition state i (M = Li^+)[5] was significant in the former but not so much in the latter (i, M = K^+), since the coordinating ability of potassium cation is much less than that of lithium cation. The anti selectivity observed in the latter case suggests that the reduction should proceed through an open-chain model. Since the selectivity of the reduction is thus assumed to be heavily influenced by a stability of i, the use of a complex metal hydride whose metal possesses a high coordinating ability is advisable for producing a still higher selectivity. Zinc borohydride[6] was presumed to be ideally suited for this purpose. In fact, when the various β-keto esters **2** were reduced with $Zn(BH_4)_2$, the desired syn compounds **1** were obtained with unexpectedly high selectivity as shown in Table I except when R^1 were alkyl groups (type 1 reduction).[7]

The $Zn(BH_4)_2$ reductions of the structurally related α-methyl-β-hydroxy ketones **4** (type 2 reduction) were also found to proceed with high selectivity (Table II).[8] Reductions of **4** with $NaBH_4$ in MeOH or $LiBH_4$ in Et_2O were also examined for comparison. Selectivities were found to be poor in both cases (syn/anti ratio, 1.5–6/1),[8] which apparently shows that a contribution of zinc cation is significant for providing high selectivity.

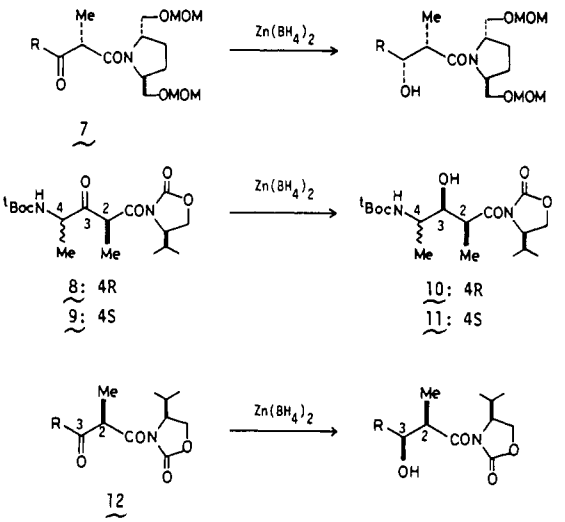
(4) Canceill, J.; Basselier, J.-J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 1024. Canceill J.; Jacques, J. *Ibid.* **1970**, 2180.
(5) Cf. Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748.
(6) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.
(7) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641.
(8) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411. This work was presented at the 101st Annual Meeting of the Pharmaceutical Society of Japan at Kumamoto, April 1981 (Abstracts of Papers, p 452). See also ref 15.

Table II
Reduction of β-Hydroxy or β-Alkoxy Ketones 4 with $Zn(BH_4)_2$ (Type 2 Reduction)



entry	R^1	R^2	*syn*-5/*anti*-6	% yield
1	Ph	Me	33/1	99
2	Ph	MEM	8.9/1	98
3	Ph	H	25/1	95
4	CH_2=C(Me)	H	25/1	91
5	$PhCH_2CH_2$	H	1.3/1	97

Scheme II
The $Zn(BH_4)_2$ Reduction of the Optically Active β-Keto Amides



It is noteworthy that the β-methoxy derivative gave a better result than the MEM derivative (entries 1,2, Table II).

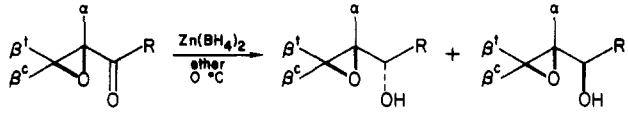
Ito and Yamaguchi[9a] recently reported that the $Zn(BH_4)_2$ reduction of α-methyl-β-keto amides produced the syn compounds with high selectivity even if the ketones were not conjugated with olefinic groups. This work was applied to the syn-selective reduction of the optically active β-keto amide **7**.[9b] Almost at the same time, DiPardo and Bock[10] reported that $Zn(BH_4)_2$ reduction of the optically active **8** and **9** gave exclusively 2*S*, 3*S* compounds **10** and **11** (<1% of the isomer), respectively (Scheme II). Moreover, Evans and coworkers[11] reported the same highly syn-selective reduction of optically active **12** and its C-2 epimer prepared by asymmetric acylation of chiral imide enolate. By these modifications, the scope of the present $Zn(BH_4)_2$ reduction was remarkably extended.

Reduction of α,β-Epoxy Ketones (Type 3 Reduction) and α-Hydroxy Ketones (Type 4 Reduction) with $Zn(BH_4)_2$

We then examined the $Zn(BH_4)_2$ reduction of α,β-epoxy ketones and α-hydroxy ketones in which the

(9) (a) Ito, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5385. (b) Katsuki, T.; Kawanami, Y.; Kitagawa, T.; Ito, Y.; Yamaguchi, M. The 26th Symposium on the Chemistry of Natural Products at Kyoto, Oct 1983 (Symposium Papers, p 453).
(10) DiPardo, R. M.; Bock, M. G. *Tetrahedron Lett.* **1983**, *24*, 4805.
(11) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

Table III
Reduction of α,β-Epoxy Ketones 13 with $Zn(BH_4)_2$ (Type 3 Reduction)



13 *anti*-14 *syn*-15

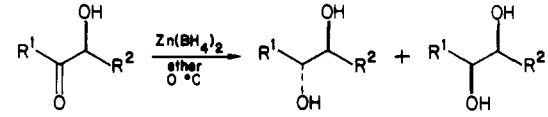
entry	R	α	β^c	β^t	*anti*-14/*syn*-15	% yield
1	Me	H	H	H	98/2	80
2	Me	Me	H	H	90/10	76
3	Me	Me	H	Me	84/16	79
4	Et	Me	H	H	99/1	76
5	Et	Me	H	Et	99/1	83
6	*n*-Bu	Me	H	H	97/3	87
7	Me	H	Me	Me	>99/<1	83
8	Me	Me	Me	Me	>99/<1	86

typical five-membered Cram's "cyclic model"[5] predicted the stereochemical outcome.

Chautemps and Pierre[12] have already studied the reduction of α,β-epoxy ketones **13** with $NaBH_4$ and have found that extremely high anti selectivity was obtained when the α-substituent was hydrogen. However, this selectivity was almost lost when this hydrogen was replaced by a methyl group. The $Zn(BH_4)_2$ reduction of **13** was again undertaken (type 3 reduction), and the results are summarized in Table III.[13] It is remarkable that anti-epoxy alcohols **14** were obtained with high selectivity irrespective of the substitution pattern of the epoxide. Recently, the $Zn(BH_4)_2$ reduction of optically active α,β-epoxy ketones was reported to afford optically active anti isomers with high selectivity.[14]

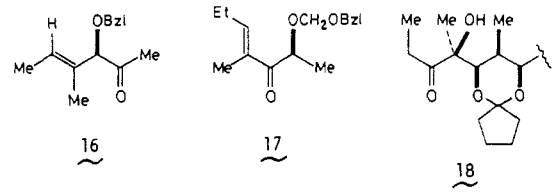
Complex hydride reduction of α-hydroxy ketones has been extensively studied. The selectivity observed in the $NaBH_4$ reduction of α-methoxy ketone [PhCOCH(OMe)Me] was unsatisfactory,[15] while the same $NaBH_4$ reduction of the corresponding *tert*-butyl α-alkoxy-β-keto carboxylate [$R^1COCH(OR^2)COO$-*t*-Bu] afforded the syn ester with excellent selectivity.[16] Reduction of α-hydroxy ketones **19** with various aluminum hydride reagents, expected to give a better result than the $NaBH_4$ reduction, has been widely investigated by Bowlus and Katzenellenborgen.[17] However, high selectivity (syn/anti ratio, 1/49) was obtained only when R^2 was *tert*-butyl and the reagent was triisobutylaluminum. Recently,the highly anti-selective reductions of **16** ($LiAlH_4$ or $NaBH_4$; anti/syn ratio, 90–95/10–5),[18] **17** ($LiAlH_4$; ratio, 98/2),[1,] and **18** ($LiAlH_4$; ratio, >20/1).[20] were reported. These results suggest that the selectivity of the reduction is affected not only by the coordinating ability of the metal hydride reagents but also by the structure of the substrates.

Table IV
Reduction of α-Hydroxy Ketones 19 with $Zn(BH_4)_2$ (Type 4 Reduction)



19 *anti*-20 *syn*-21

entry	R^1	R^2	*anti*-20/*syn*-21
1	*n*-C_5H_{11}	CH_3	77/23
2	*n*-C_4H_9	C_2H_5	89/11
3	*n*-C_3H_7	*n*-C_3H_7	>99/<1
4	C_2H_5	*n*-C_4H_9	87/13
5	CH_3	*n*-C_5H_{11}	85/15
6	*i*-C_3H_7	CH_3	85/15
7	CH_3	*i*-C_3H_7	96/4
8	Ph	CH_3	98/2
9	CH_3	Ph	90/10



16 17 18

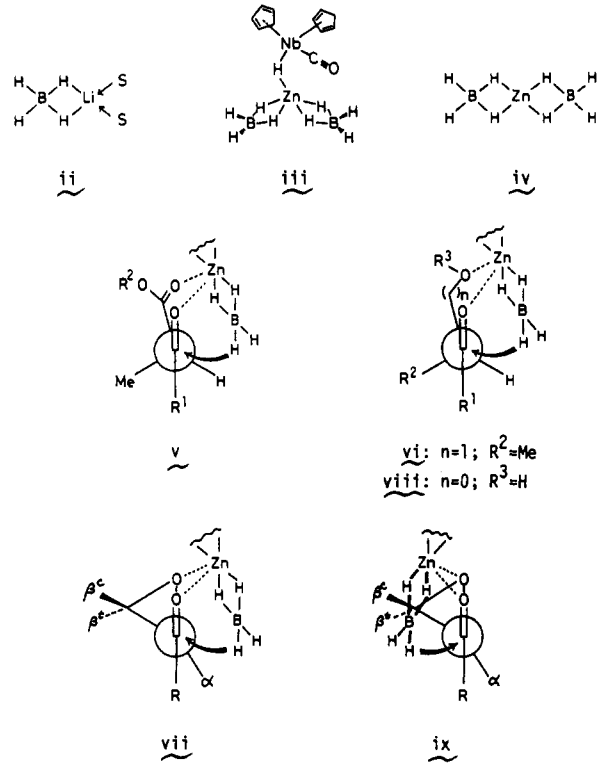
Independent of the related recent results, the $Zn(BH_4)_2$ reduction of the various α-hydroxy ketones **19** (type 4 reduction) was undertaken, and the relation between the substitution pattern of the α-hydroxy ketones and the stereoselectivity of the reduction was examined.[21a] The results are shown in Table IV. The expected anti selectivity was excellent when R^1 was phenyl (entry 8) or R^2 was isopropyl (entry 7). It should be noted that the same highly anti-selective reduction of α-(benzyloxy)methoxy ketones [(benzyloxy)methyl ether of **19**, R^2 = *i*-Pr] with $Zn(BH_4)_2$ was achieved by McGarvey and Kimura[21b] almost at the same time.

Scope of the $Zn(BH_4)_2$ Reduction of the Functionalized Ketones

The reacting species of $LiBH_4$ and $LiAlH_4$ in diethyl ether have been suggested to be a contact ion pair[22] (see ii), and the structure of $Cp_2Nb(CO)H{\cdot}Zn(BH_4)_2$ has been established as iii by X-ray crystallography,[23] the zinc atom being linked with BH_4 through pairs of hydrogen atoms.

Taking account of the above crystallography data, the reacting species of $Zn(BH_4)_2$ is considered to be a contact ion pair iv. Thus the gross structure of the transition states of the type 1–4 reductions may be schematically shown as v, vi, vii, and viii, respectively.

(12) Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549.
(13) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, *22*, 4723.
(14) Banfi, S.; Colonna, S.; Molinari, H.; Julia, S. *Synth. Commun.* **1983**, *13*, 901.
(15) Yamada, S.; Koga, K. *Tetrahedron Lett.* **1967**, 1711. Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1972**, *20*, 526.
(16) Glass, R. S.; Deardorff, D. R.; Henegar, K. *Tetrahedron Lett.* **1980**, *21*, 2467.
(17) Bowlus, S. B.; Katzenellenborgen, J. A. *J. Org. Chem.* **1974**, *39*, 3309. See also: Stocker, J. H.; Sidisuntlorn, P.; Benjamin, B. M.; Collins, C. J. *J. Am. Chem. Soc.* **1960**, *82*, 3913.
(18) Tokuyama, T.; Shimada, K.; Uemura, M.; Daly, J. W. *Tetrahedron Lett.* **1982**, *23*, 2121.
(19) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355.
(20) Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686.
(21) (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653. This work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan at Osaka, April 1982 (Abstracts of Papers, p 405) and at the 41st Symposium on the Synthetic Organic Chemistry at Tokyo, June, 1982 (Proceedings, p 29). (b) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5422.
(22) (a) Ashby, E. C.; Dobbs, F. R.; Hopkins, H. P., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 3158. (b) Boone, J. R.; Ashby, E. C. "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Ed.; Wiley: New York, 1979; Vol. 11, p 53.
(23) Porai-Koshits, M. A.; Antsyshikina, A. S.; Pasynskii, A. A.; Sadikov, G. G.; Skripkin, Yu. V.; Ostrikova, V. N. *Inorg. Chem. Acta* **1979**, *34*, L 285.



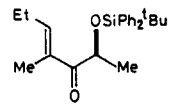
The selectivity should be related to the stability of these zinc-mediated transition states. Extremely high selectivities were obtained when R^1 were phenyl or vinyl groups (type 1, 2, and 4 reductions) or when the esters in α-methyl-β-keto esters **2** were replaced by the amides (reductions of **7**, **8**, **9**, and **12**; type 1 reduction). These results can be attributed to the increased coordinating ability of the β-keto or amide carbonyl groups due to the conjugation with the unsaturated systems in the former or the electron-donating nitrogen atom in the later.

In type 3 reductions, selectivities were excellent irrepective of the substitution pattern of epoxides (Table III). In type 4 reductions when R^2 was the branched isopropyl group, high anti selectivity was obtained (entry 7, Table IV) even if R^1 was methyl.[24] These results can be explained by considering that an initial approach of the sterically demanding $Zn(BH_4)_2$ from the β-carbon side of epoxide or the isopropyl group side is interrupted by these bulky groups. Particularly, predominant hydride transfer from the same side of the α-methyl group of epoxides **13** (entries 2–6, 8, Table III) can only be explained by taking account of the advantage of the transition state vii over ix.

Reduction of α-Hydroxy Ketones through Open-Chain Model (Type 5 Reduction)

The 1,2-asymmetric induction reactions so far mentioned are presumed to proceed through Zn-mediated cyclic transition states. We then examined the reductions where open-chain model should be involved.

Although several models have been proposed,[25] the Felkin[26] –Anh[27] model is considered to be the most probable. In this model, the favored conformers are presumed to be those where the largest or electron-withdrawing α-substituents are located perpendicularly to the carbonyl group. An excellent example of such a reaction was recently reported when, in the course of synthetic studies on pumiliotoxin B, Overman and McCready[19] succeeded in the highly syn-selective reduction of α-(*tert*-butyldiphenylsilyl)oxy ketone **22** with

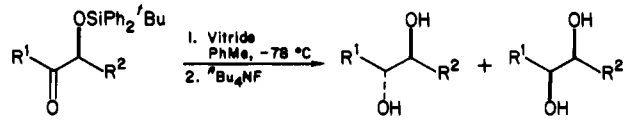


22

i-Bu_3Al in pentane or $LiAlH_4$ in THF. The syn/anti ratios of the resulting α-silyloxy alcohols were 94/6 in the former case and 95/5 in the latter case. It should be noted that the bulky hydroxyl masking group was selected so that the α-substituents should meet Felkin–Anh predictions.

Independent of this work, we extensively studied the reduction of α-(*tert*-butyldiphenylsilyl)oxy ketones **23**.[21a] We thought that complex metal hydrides whose metals have low coordinating ability would be preferable in this type of reduction. After several reagents had been tested, sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) was found to be a reagent of choice (type 5 reduction). The results are shown in Table V.[21a]

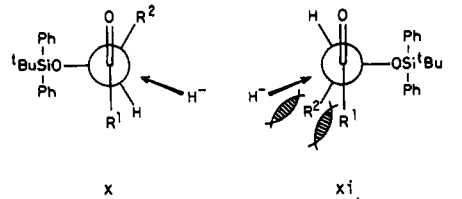
Table V
Reduction of α-Silyloxy Ketones 23 with $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Type 5 Reduction)



23 *anti*-**20** *syn*-**21**

entry	R^1	R^2	*anti*-20/*syn*-21
1	n-C_5H_{11}	CH_3	39/61
2	n-C_4H_9	C_2H_5	14/86
3	n-C_3H_7	n-C_3H_7	14/86
4	C_2H_5	n-C_4H_9	7/93
5	CH_3	n-C_5H_{11}	2/98
6	i-C_3H_7	CH_3	54/46
7	CH_3	i-C_3H_7	4/96
8	Ph	CH_3	9/91
9	CH_3	Ph	24/76

When R^2 is bulky, reduction is expected to proceed through conformer x since conformer xi leading to the anti-glycol **20** should be destabilized due to the interaction with R^1. Moreover, since an attack of nucleo-



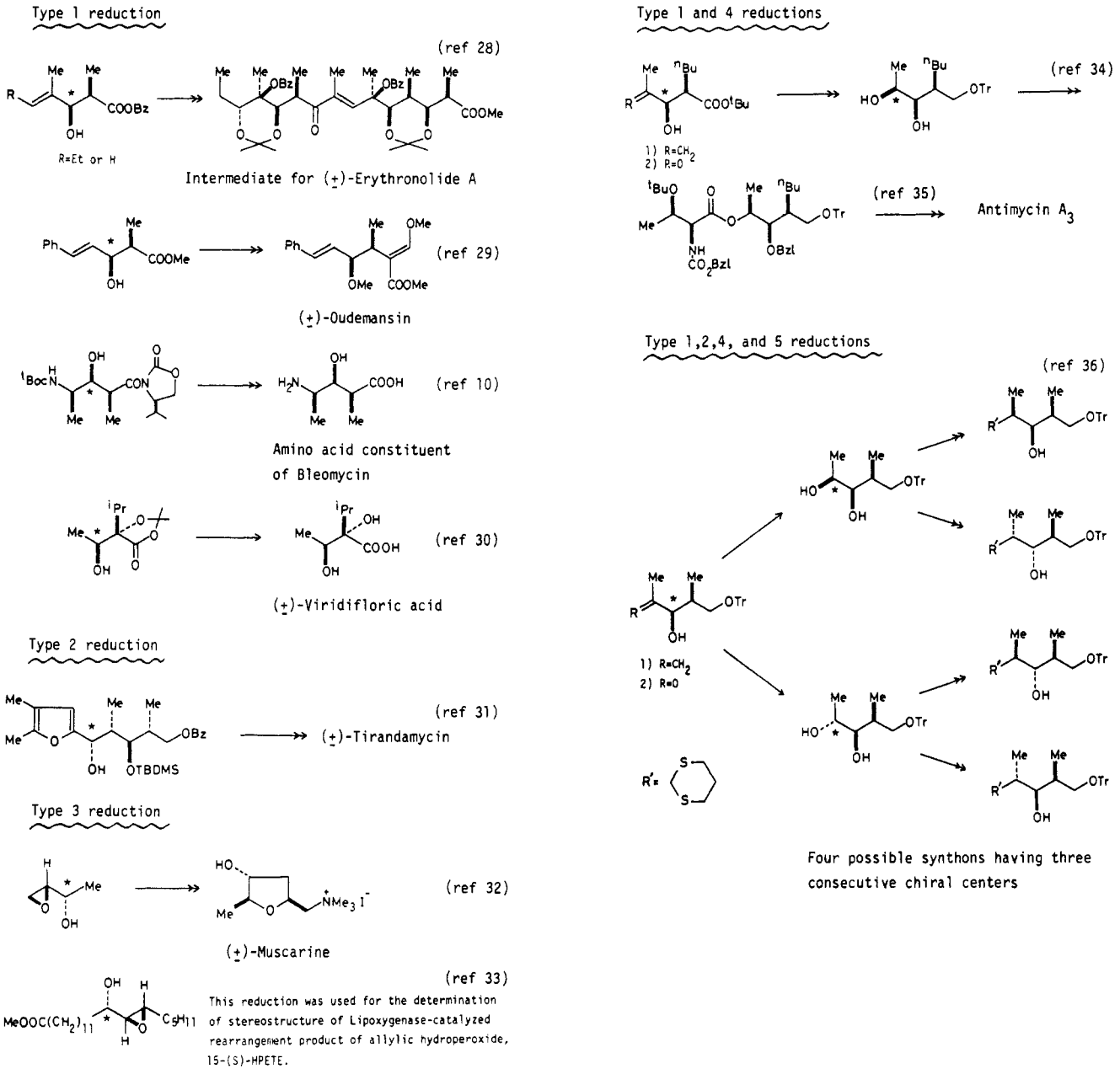
(24) The same trend was also observed in the $Zn(BH_4)_2$ reduction of α-alkyl-β-keto esters: α-Isopropyl-β-keto butyrate affords the corresponding syn isomer with high selectivity; unpublished data from our laboratory.

(25) Cf.; (a) Yamada, S.; Koga, K. "Selective Organic Transformation"; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1970, Vol. 1, p 1. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1.

(26) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

(27) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, 61. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

Scheme III
Application of the Type 1–5 Reductions for the Synthesis of Natural Products and the Related Compounds



philes on the carbonyl carbon is claimed to take place nonperpendicularly,[27] an approach of reducing agents is prevented by R^2 in xi. In fact, when R^2 is isopropyl and even when R^2 are normal alkyl groups having more than four carbon atoms, high syn selectivities were obtained (entries 4, 5, 7, Table V). However, when R^1 is a bulky isopropyl group, a poor result was observed (entry 6, Table V), which suggests that the Felkin–Anh model is no longer valid in this case because the interaction of R^1 with the still bulky (*tert*-butyldiphenylsilyl)oxy group is becoming serious with increasing bulk of R^1. However, when R^1 is phenyl (entry 8, Table V) or an olefinic group (compound 22), the syn compounds were obtained in reasonable (91/9) or high (95/5) selectivity. Since a phenyl ring or a double bond conjugated with the carbonyl group is fixed in the same plane and thus the interaction with the silyloxy group is presumed to be much less than when R^1 are bulky alkyl groups, the Felkin–Anh model again becomes valid in these cases. A severe interaction between R^2 and the olefinic proton is observed in xi, and thus the preferred conformer should be x giving syn isomers.

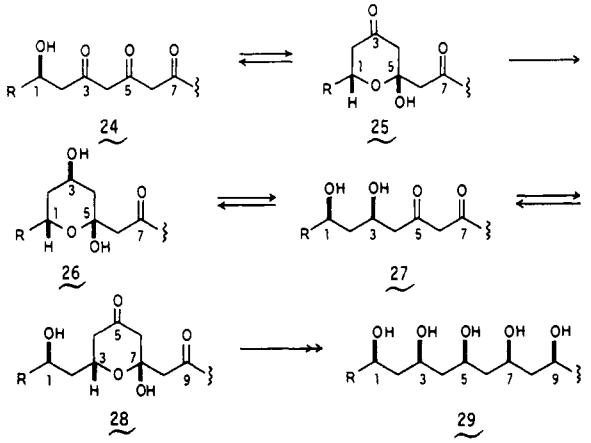
Applications

The aforementioned type 1–5 reductions have been successfully applied for the synthesis of natual products or related compounds. Only the starting materials and the target compounds are shown (Scheme III). The hydroxyl groups marked with asterisks in the starting materials are those derived from the corresponding ketones by the present methods.

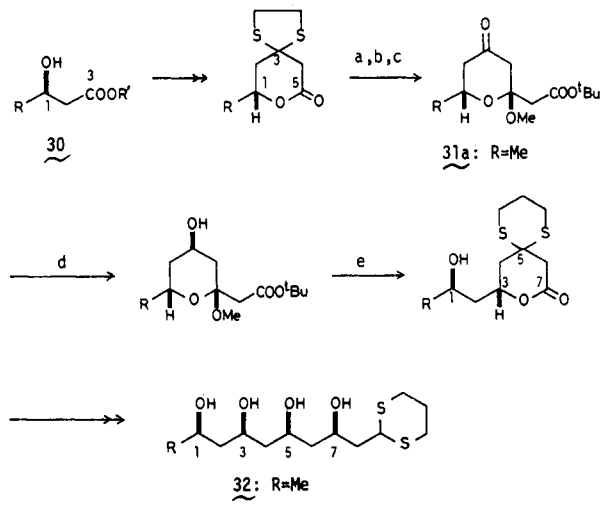
Stereoselective Synthesis of 1,3-Polyol Systems

Stereocontrolled reactions in acyclic systems have been extensively studied, and remarkable progress has been made in recent years. In many of these reactions, metal-mediated cyclic transition states play an important role, and therefore, in principle, a well-established

Scheme IV
Hypothetical Pathway for the Formation of 1,3-Polyol

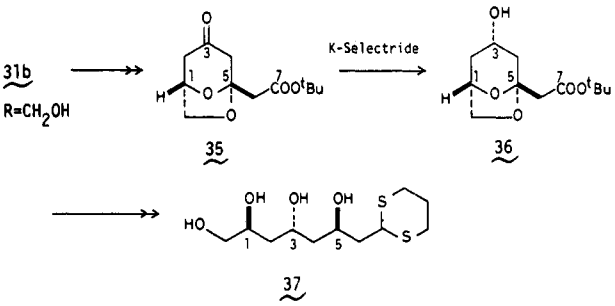


Scheme V
Synthesis of *syn*-1,3,5,7-Tetrol Derivative



a) LDA/CH_3COO^tBu/THF, b) $CH(OMe)_3$/CSA/CH_2Cl_2/MeOH, c) NBS/$AgNO_3$/Na_2CO_3/aq MeCN, d) K-Selectride/THF, e) 1,3-Propanedithiol/$BF_3 \cdot Et_2O$/CH_2Cl_2

Scheme VI
Synthesis of *anti*-1,3,5-Triol Derivative



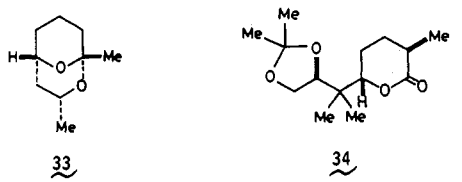
stereochemistry in cyclic systems is still valid even in these reactions.

Keeping these general trends in mind, we considered that if it was possible to design multifunctionalized acyclic ketones that were in equilibrium with their cyclic form, and if the latter form existed predominantly during the reduction, then acyclic alcohols would be obtained with high stereoselectivity.

1,3-Polyol functions are often found in polyene macrolide antibiotics or in related natural products, and the development of their synthetic methodology is under extensive investigation.[37] These polyols are presumed to be produced biogenetically from polyketide precursors by the NADPH-promoted enzymatic reduction although the details are not known at present. Our working hypothesis for 1,3-polyol synthesis is related to this biogenetic pathway and is based on the strategy of introducing hydroxyl groups to the acyclic system. The outline is schematically shown in Scheme IV.[37]

The 1-hydroxy-3,5-dioxo derivative **24**, which is expected to be derived from 1,3-polyketide, may be in equilibrium with the cyclic hemiacetal **25**, the later predominating. Reduction of the C_3-ketone of **25** may take place from the less hindered α-side, exclusively affording **26**, which is convertible to the corresponding ring-opened form **27** having a 1,3-*syn*-diol moiety. The recyclization between C_3-hydroxyl and C_7-keto groups of **27** would afford **28**, whose six-membered hemiacetal moiety is similar to that of **25**. The repetition of a series of reactions—reduction, ring opening, and recyclization—would produce *syn*-1,3-polyols **29** stereoselectively. It is noteworthy that the six-membered hemiacetal moiety that is playing a crucial role in the above scheme is involved in natural products such as amphotericin, pederin, aplasmomycin, and boromycin.

We intended to synthesize *syn*-1,3-polyols by modifying the above hypothetical pathway to a more practical one, while retaining the same principle. Thus, *syn*-1,3,5,7-tetrol derivative **32** was synthesized with virtually complete stereoselection as shown in Scheme V.[37] The starting β-hydroxy esters **30** can be easily obtained in optically active form either from naturally occurring resources or by the enantioselective microbiological reduction of the corresponding keto esters.[38] Using this methodology, we have synthesized the optically active compound **33**[39] isolated from Norway spruce infested by *Trypodendron lineatum* Oliv. and lactone **34**, an important segment of aplasmomycin and boromycin.[40]



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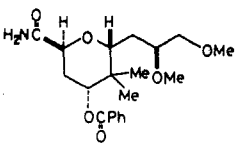
(40) Nakata, T.; Nagao, S.; Mori, N.; Oishi. T., presented at the 104th Annual Meeting of Pharmaceutical Society of Japan at Sendai, March 1984 (Abstracts of Papers, p 280).

The synthesis of *anti*-1,3-polyols was achieved by slightly modifying the above scheme. The reduction was carried out after the ketone **31b** had been transformed into the bicyclic compound **35** so that the hydride anion should attack the carbonyl group exclusively from the less hindered β-side (Scheme VI). The desired *anti*-1,3,5-triol **37** could be derived easily from the reduction product **36**.[41]

Combining the newly developed methods for *syn*- and *anti*-1,3-polyol synthesis, we recently succeeded in the synthesis of (+)-pedamide (**38**),[42] a right half of (+)-pederin, under virtually complete stereoselection.



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Conclusion and Future Prospects

Stereoselective reductions of acyclic ketones, which began with those of α-methyl-β-keto esters, have been extended far more than initially anticipated. It has become possible to deduce a relation between the substitution pattern of the ketone and the stereoselectivity of the reduction.

We have also demonstrated in this Account the stereoselective synthesis of *syn*- and *anti*-1,3-polyols. A set of reactions involved in the initial 1,3-diol synthesis can be repeatedly used for the synthesis of the higher analogues, which would allow the present method to be applied widely to the synthesis of ionophore, polyene, or related macrolide antibiotics.

We are grateful to our collaborators whose names are listed in the references. We also thank a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

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