ASYMMETRIC INDUCTION IN THE INTRAMOLECULAR CONJUGATE ADDITION OF γ- OR δ-CARBAMOYLOXY-α,β-UNSATURATED ESTERS. A NEW METHOD FOR DIASTEREOSELECTIVE AMINATION AND DIVERGENT SYNTHESES OF 3-AMINO-2,3,6-TRIDEOXYHEXOSES#

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Abstract— Prominent 1,2- and 1,3-asymmetric induction in the intramolecular conjugate addition of γ- or δ-carbamoyloxy-α,β-unsaturated esters provides a new method for diastereoselective amination of acyclic olefinic systems, which has been applied to stereocontrolled divergent syntheses of 3-amino-2,3,6-trideoxyhexoses. Factors controlling the stereochemistry are discussed, and related cyclizations are also described.

CONTENTS

Dedicated to Prof. Sir Derek Barton on the occasion of his 70th birthday.

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1. Introduction

The stereocontrolled synthesis of biologically important amino alcohols such as deoxyaminosugars (Figure 1) from noncarbohydrate precursors is currently receiving considerable attention.[1] There are two basic approaches for it. One is the concomitant generation of alcohol and/or amine functionality with carbon-carbon bond formation.[2] The other is a functionalization of the olefinic systems after construction of their carbon frameworks.[3] We have been interested in the latter approach, particularly the direct addition of a nitrogen functionality to an acyclic unsaturated alcohol system, since it has not generally been as stereoselective[3a] as the two-step procedure, asymmetric Sharpless' epoxidation of allylic alcohols and subsequent addition of nitrogen nucleophiles.[3b] We focus this review on our recent development and application of the diastereoselective amination mediated by intramolecular conjugate addition of carbamate groups.[4-11]

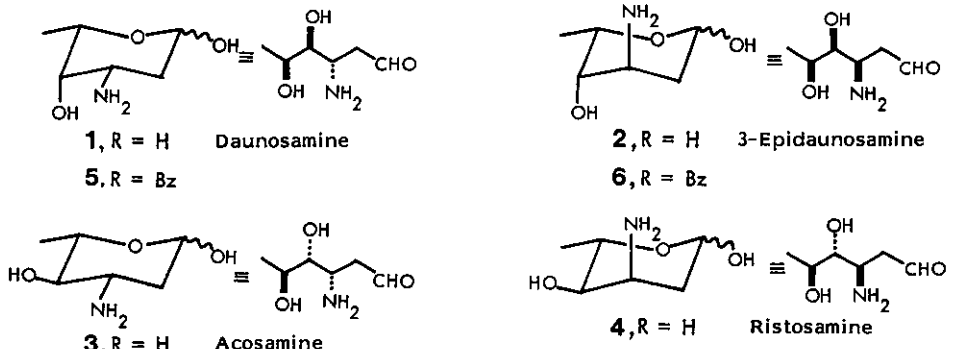


Figure 1

The long known conjugate addition of ammonia and amines to α, β-unsaturated carbonyl compounds is a very convenient procedure to introduce amino functionality to the β-position of carbonyl groups.[12] However, they often suffer from sluggish rate of reaction, low yield, and low stereoselectivity, particularly in the addition of ammonia[12-16] (Figure 2).[$] In order to overcome these problems we tried

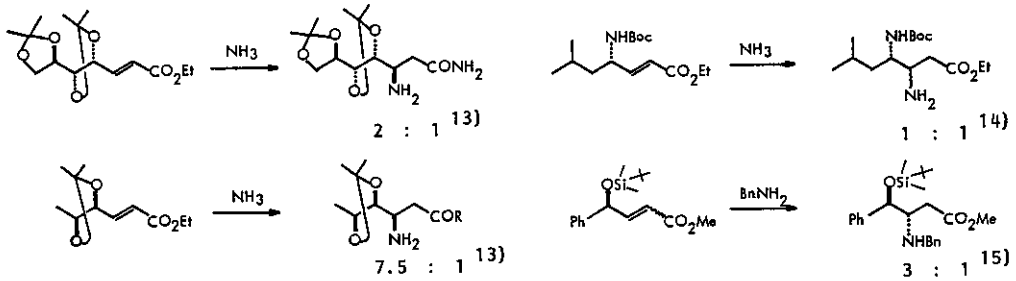


Figure 2

$ In all figures, only major products are shown.

to take advantage of intramolecular reactions, which are generally ten to the several times faster than the corresponding intermolecular processes due to the small activation entropy,[17] and may have greater diastereoface selectivity owing to the decreased conformational freedom in their transition states. Thus, we expected that an ambident[18] carbamate group would cyclize quickly and stereoselectively at anionic nitrogen under basic conditions[19] (Figure 3). With these anticipation, the stereoselectivity and its controlling factors have been first examined.

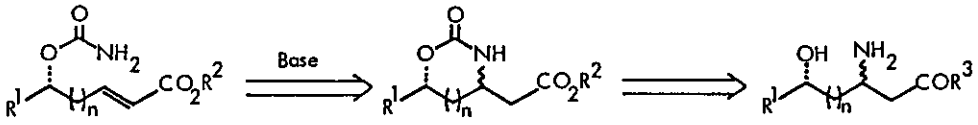


Figure 3

2. Conjugate Addition of γ-Carbamoyloxy-α, β-unsaturated Esters

When γ-carbamoyloxy- α, β-unsaturated esters **9-15** were stirred with 1.0 molar equiv. of t-BuOK at 0°C in dry THF under argon atmosphere, rapid cyclizations occurred via nitrogen producing mainly the trans-oxazolidinones, which correspond to 1,2-syn amino alcohols (Figure 4).[4,9] The rate of the reaction highly depends on the kind of the base used: very rapid with t-BuOK and KH, slow with NaH, and slower with LiH, while the stereoselectivity is not affected by changing the reaction period or the base. The cyclizations occurred and similar stereoselec-

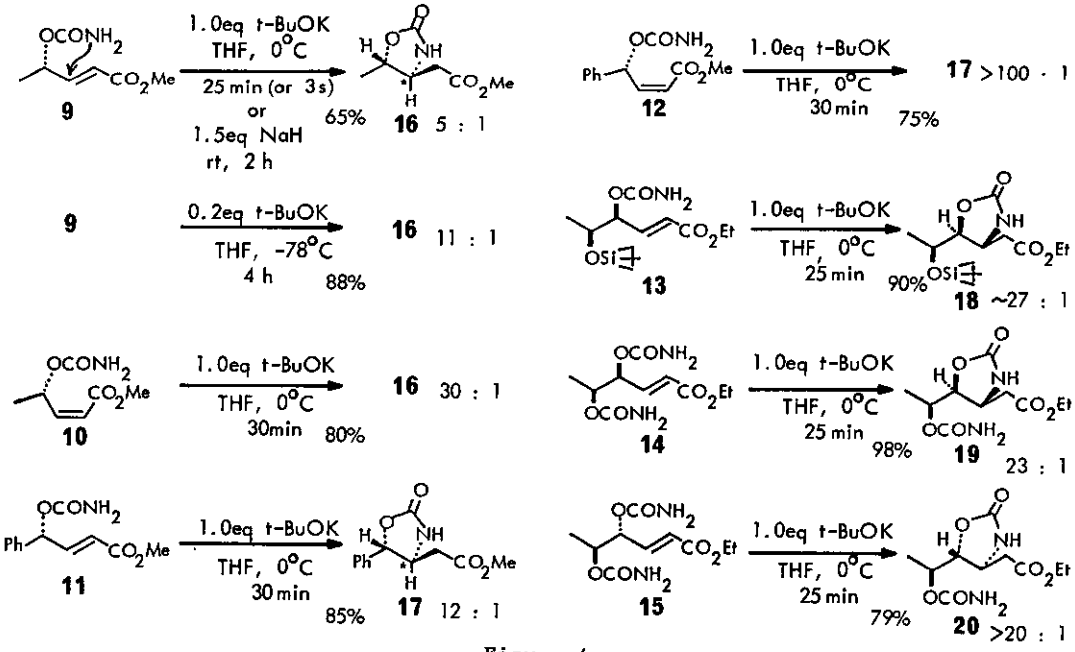


Figure 4

tivity was achieved, even with 0.1 molar equiv. of base, though the reactions did not always complete under such conditions. Higher 1,2-asymmetric induction was observed for the reaction at lower temperatures and for the compounds with more sterically demanding groups. Dramatic increase of syn-selectivity was observed, when the Z olefin was used. In the competitive cyclization between allylic and homoallylic carbamate groups, the former added more rapidly. Thus, 5-Exo-Trig mode of cyclization has proven to be faster than 6-Exo-Trig.[20] All of these results support that the reaction occurs under kinetic control.

The observed 1,2-syn selectivity is explicable on the basis of allylic strain.[21] (Figure 5). Between two possible transition states **A** and **B** satisfying the required trajectory of nucleophile for 5-Exo-Trig closure,[22] **A** leading to syn product should be favored because **B** involves a larger allylic 1,3-strain.[21] The severe allylic strain in **B(Z)** from **12** should allow the exclusive formation of **17**. Thus, $\Delta\Delta G^{\ddagger}$ calculated from the product ratios should be originated from as the corresponding allylic 1,3-strains.

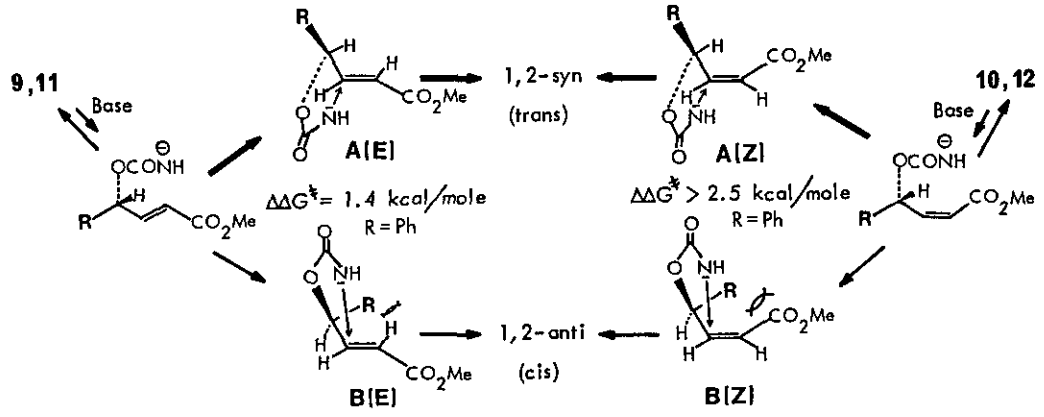


Figure 5

Since the cyclization of carbamate anion generated with t-BuOK completes in an instant in spite of its very low formation constant ($K \leq 10^{-6}$),[23] so called proximity effect[17] is likely to be essential for the reaction. This was supported by the following experiments. The intermolecular addition of t-butyl- or phenylcarbamates to α,β-unsaturated esters in the presence of strong bases did not occur,[15] nor did the intramolecular cyclization of methyl 6-carbamoyloxy-2-heptenoate (bishomoallylic carbamates),[15] whereas δ-carbamoyloxy-α,β-unsaturated esters (homoallylic carbamates) cyclized smoothly as discussed in the next section.

3. Conjugate Addition of δ-Carbamoyloxy-α, β-unsaturated Esters

Homoallylic carbamates also cyclized smoothly with NaH to 6-membered cyclic carbamates with high 1,3-syn-asymmetric induction (Figure 6).[4,9] The presence of a Z double bond also improved the stereoselectivity to a large extent.

Two transition state models **C** and **D** might be most plausible for the 1,3-syn and 1,3-anti cyclizations, respectively, considering the conformational stability of carbon chain[24] and the trajectory of nucleophilic attack to a double bond[22,25] (Figure 7). As nonbonded interaction around C3-C4 bond is identical between **C** and **D**, larger gauche interaction (Me-C3) around C4-C5 bond in **D** than those (Me-H, C3-H) in **C** should be responsible for the observed syn selectivity.

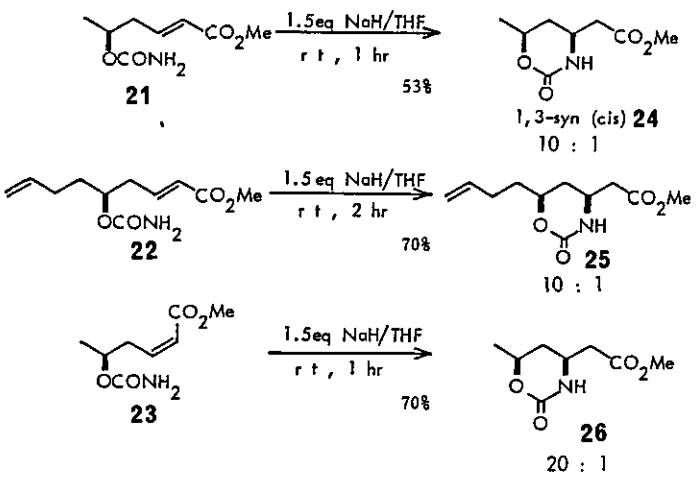


Figure 6

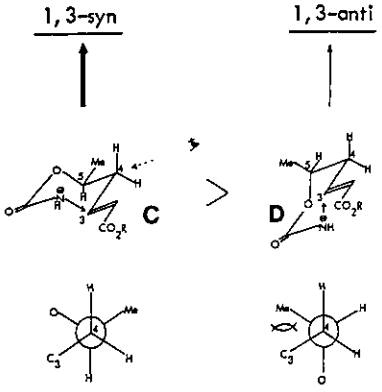


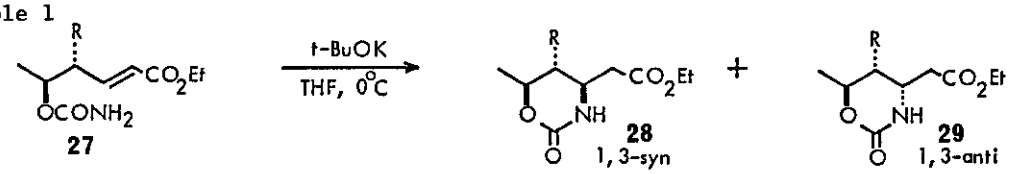
Figure 7

4. Effect of γ-Substituent on Diastereoselectivity in the Reaction of δ-Carbamoyloxy-α, β-unsaturated Esters

The 1,3-diastereoselectivity in the cyclization described in section 3 was affected by an additional oxygen function (R) at the γ-position. The R group in the anti (erythro) orientation to the δ-carbamoyloxy group increased the apparent 1,3-syn selectivity as shown in Table 1 except t-BuO group.[4,5,9]

This increased diastereoselectivity can not be explained in terms of the gauche interaction alone, because by replacing H_4 by OR there is an additional gauche repulsion between methyl and O(R) created in **E**, and a favorable interaction, so called gauche effect, between two oxygens[26] in **F** (Figure 8). As the result, **F** would be more stabilized relative to **E** than **D** to **C**, and the 1,3-syn selectivity would be decreased in these cases as compared with **21**.

Table 1



Substrate	Yield	Ratio
21 R = H (NaH)	53%	10 : 1
27a R = O^{t}Bu	91%	7 : 1
b R = OMe	90%	18 : 1
c R = OAc	52%	19 : 1
d R = OSiMe$_2$^{t}Bu	90%	36 : 1
e R = OSiEt$_3$	74%	50 : 1

Thus, we have to consider the interactions between the incoming nucleophile and the γ-substituent adjacent to the reaction center, i.e. steric, electrostatic and stereoelectronic effects.[25] The last one seems to be a most important controlling factor, because t-butyl ether (**27a**), which is assumed to have the largest steric and electrostatic effects, gave the lowest ratio in the series. The result is best explained by stereoelectronic effect. LUMO of the unsaturated ester in **E** would be stabilized by its orbital interaction with σ* orbital of the C4-O bond and result in the better stereoelectronic interaction with HOMO of nucleophile approaching from anti direction (antiperiplanar effect),[25] whereas such an effect can not be expected in **F** where the nucleophile and the C-O bond are synclinal (Figure 9). Thus, provided that the C4-O σ* orbital of silyl ethers (**27d,e**) is lower than that of the alkyl ethers (**27a,b**) as in acetate (**27c**),[27] the larger LUMO-LUMO interaction and therefore the higher selectivity is expected. The better ratios in Et_3Si ethers (**27e** and **30a**) in Table 1 and 2 (vide infra) suggest its more demanding steric requirement than t-BuMe_2Si group.[5]

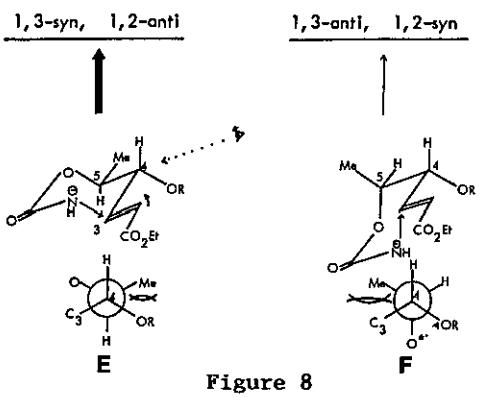
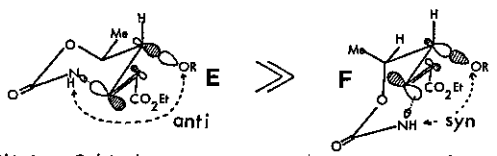


Figure 8



Stabilizing Orbital Interaction in the Transition State

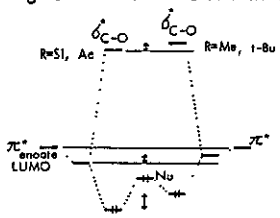
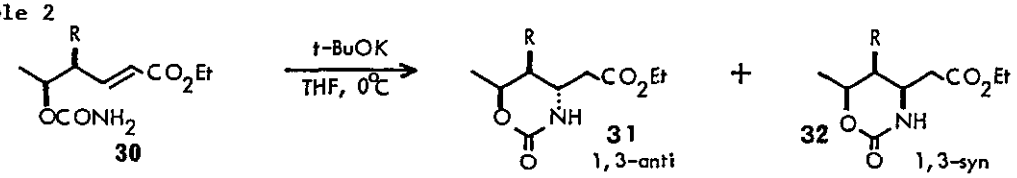


Figure 9

On the other hand, when the oxygen function is in the syn (threo) orientation as in **30**, the gauche interactions around C4-C5 should be in favor of **G** over **H**, but the stereoelectronic stabilization operates only in **H** (Figure 10). Thus, with these counteracting effects, stereoselectivity should be lower in this case than in 27.[9] The results shown in Table 2 is in accord with the prediction. The 1,3-anti selectivity indicates the latter effect has a larger contribution than the former.[5]

Table 2



Substrate	Yield	Ratio
30a R = $OSiEt_3$	75%	5 : 1
b R = $OSiMe_2{}^tBu$	53%	2 : 1

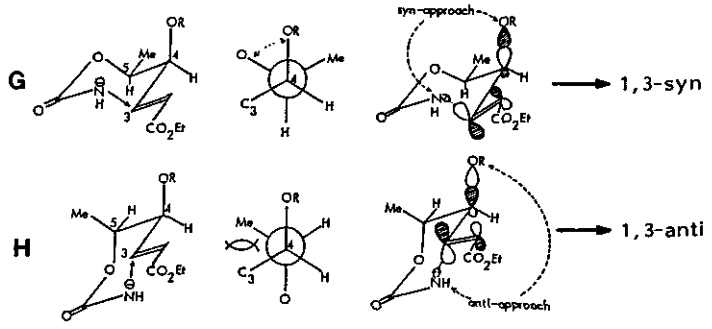
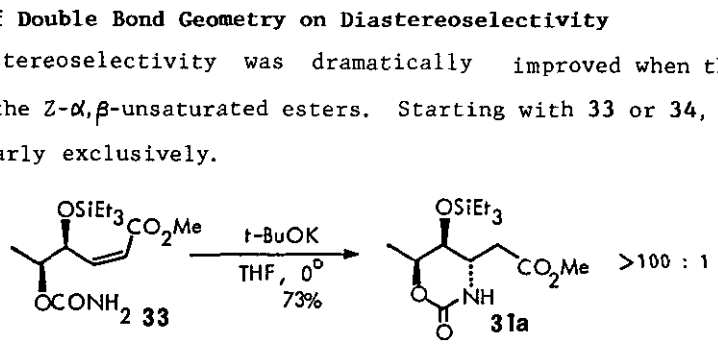


Figure 10

5. Effect of Double Bond Geometry on Diastereoselectivity

The above stereoselectivity was dramatically improved when the reaction was applied to the Z-α,β-unsaturated esters. Starting with **33** or **34**, **31a** or **28e** was obtained nearly exclusively.



The selectivity can be rationalized by assuming the transition states **I** and **J** (Figure 11).[8,9] In these transition states, conformations are more rigid than in those (**E** and **H**) of the E-isomers, and the double bond in each lies in a favorable direction for stereoelectronic interaction, because of the large repulsion between the bulky $OSiEt_3$ and the CO_2Me directing inward.

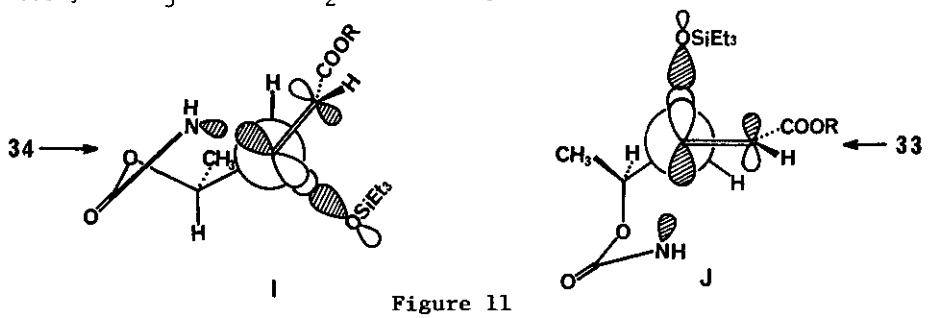


Figure 11

6. Complementary Diastereofacial Selection

These reactions provide a good way to achieve diastereoselective amination of acyclic olefinic systems, since the complementary diastereofacial selection can be accomplished by changing the site of carbamoyloxy group between γ- and δ-positions as summarized in Figure 12. Its synthetic utility has been demonstrated by the stereoselective syntheses of all four possible diastereomers of racemic N-acyl-3-amino-2,3,6-trideoxyhexoses (Figure 13-16).[5,6]

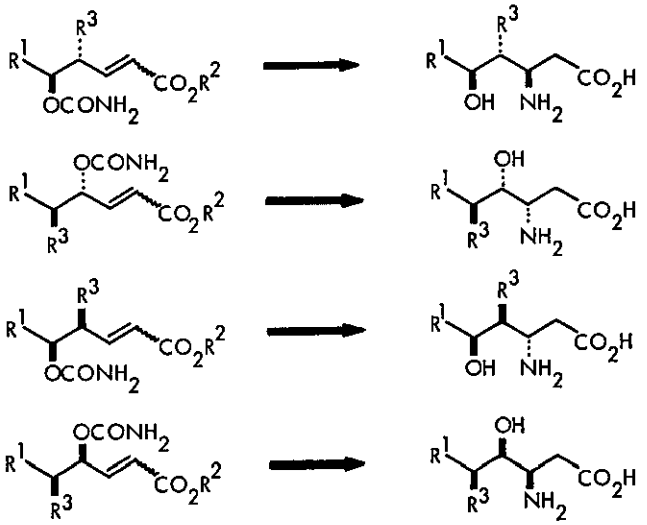
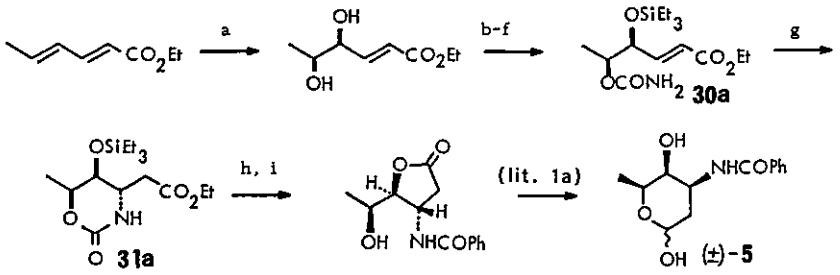
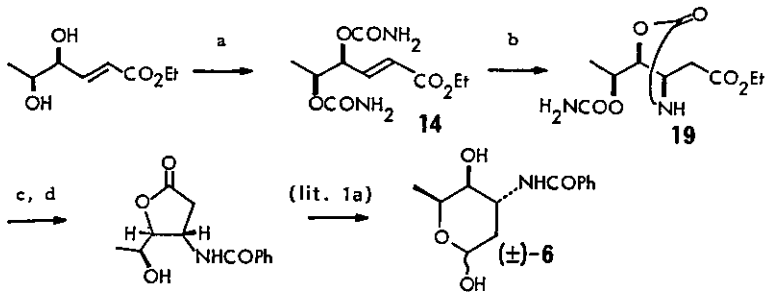


Figure 12



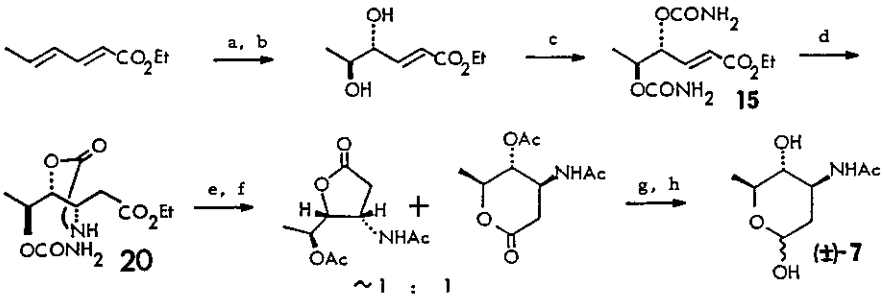
(a) Cat. OsO_4,N-Methylmorpholine Oxide(32%);(b) $ClSiMe_2$t-Bu(49%);(c) DHP(94%);
(d) n-Bu_4NF(100%);(e) $ClSO_2NCO;H_2O$,70°C(100%);(f) Et_3SiCl(79%);(g) t-BuOK(75%);
(h) 1N-NaOH,60°C;(i) $PhCOCl,NaHCO_3$(53%)

Figure 13. Synthesis of (±)-N-Benzoyldaunosamine



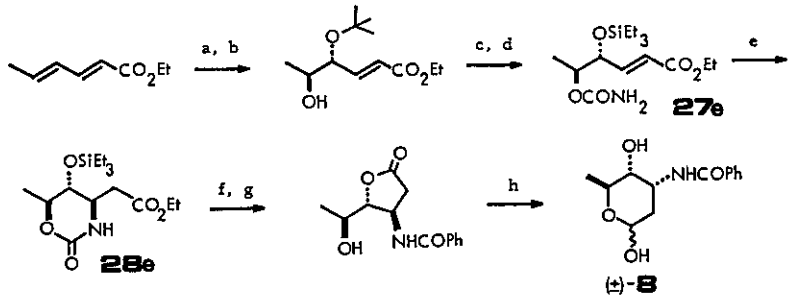
(a) $ClSO_2NCO;H_2O$,70°C(63%);(b) t-BuOK(98%);(c) 1N-NaOH,60°C;
(d) $PhCOCl,NaHCO_3$(61%)

Figure 14. Synthesis of (±)-N-Benzoyl-3-epidaunosamine



(a) MCPBA(82%);(b) 0.14N-$HClO_4$(92%);(c) $ClSO_2NCO$,-20°C; H_2O,70°C(63%);(d) t-BuOK(79%);
(e) 1N-NaOH,60°C;(f) Ac_2O, rt-60°C(79%);(g) DIBAL,THF,-50°C;(h) 1N-NaOH,MeOH(44%)

Figure 15. Synthesis of (±)-Acetylacosamine



(a) MCPBA(82%);(b) $BF_3 \cdot OEt_2$,t-BuOH(56%);(c) $ClSO_2NCO$,-20°C;H_2O,70°C(70%);
(d) Et_3SiCl,DMF,imidazole(92%);(e) t-BuOK(74%);(f) 1N-NaOH,60°C;(g) PhCOCl(51%);
(h) DIBAL,-78°C(43%)

Figure 16. Synthesis of (±)-Benzoylristosamine

7. Synthesis of L-N-Benzoyldaunosamine

The 3-amino-2,3,6-trideoxyhexoses such as daunosamine (**1**),[28] acosamine (**3**)[29] and ristosamine (**4**)[30] are distributed in nature as the glycosidic moiety of important antibiotics and their syntheses have been the focus of considerable attention in recent years.[1] However, there is no stereocontrolled divergent synthesis of these isomeric sugars from common intermediate without the aid of stereochemical inversion procedures.

N-Benzoyl derivative **5** of daunosamine (**1**), found in anthracycline antibiotics such as adriamycin used clinically in antitumor therapy,[28] was synthesized[1] from L-lactaldehyde derivative **35** by using our amination methodology (Figure 17).[7]

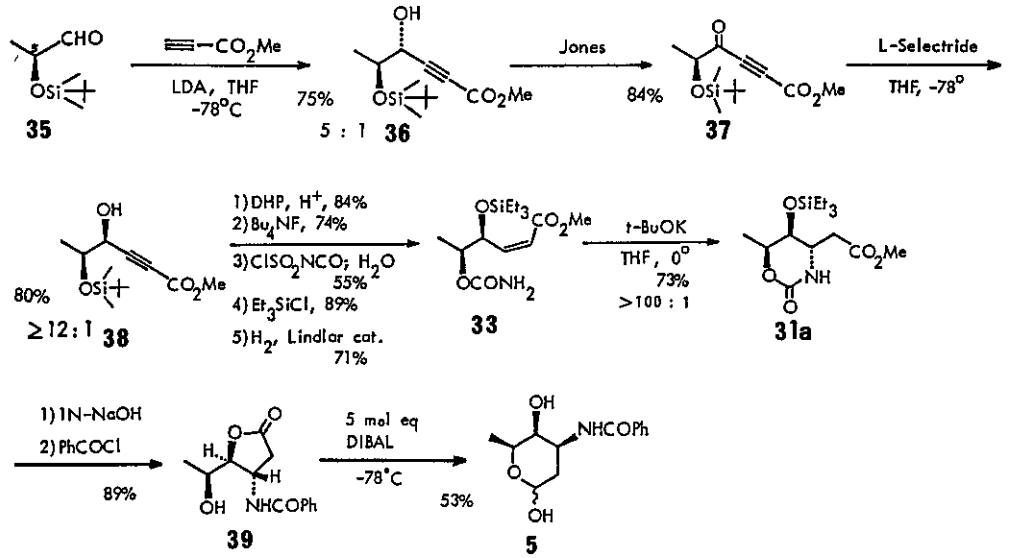


Figure 17

The threo-diol derivative **38** was synthesized as a major isomer (≥12:1) from O-(t-butyldimethylsilyl)lactaldehyde **35** and methyl propiolate via coupling and oxidation followed by stereoselective reduction with L-Selectride. The compound **38** was converted into the key intermediate **33** in five steps, which was then subjected to intramolecular conjugate addition to give the 1,3-anti (1,2-anti) product **31a** exclusively (>100:1) as discussed above. Alkaline hydrolysis of **31a** and subsequent benzoylation afforded the known L-lyxo-γ-lactone **39**, which was then reduced to L-N-benzoyldaunosamine **5**.[7]

8. Synthesis of L-N-Acetylacosamine

Acosamine (**3**) was originally isolated as one of the sugar constituents of actinoidin,[29] a member of the important vancomycin group of glycopeptide antibiotics, and is of synthetic interests[1] since the replacement of daunosamine in adriamycin by acosamine was reported to reduce the cardiotoxicity retaining the anticancer

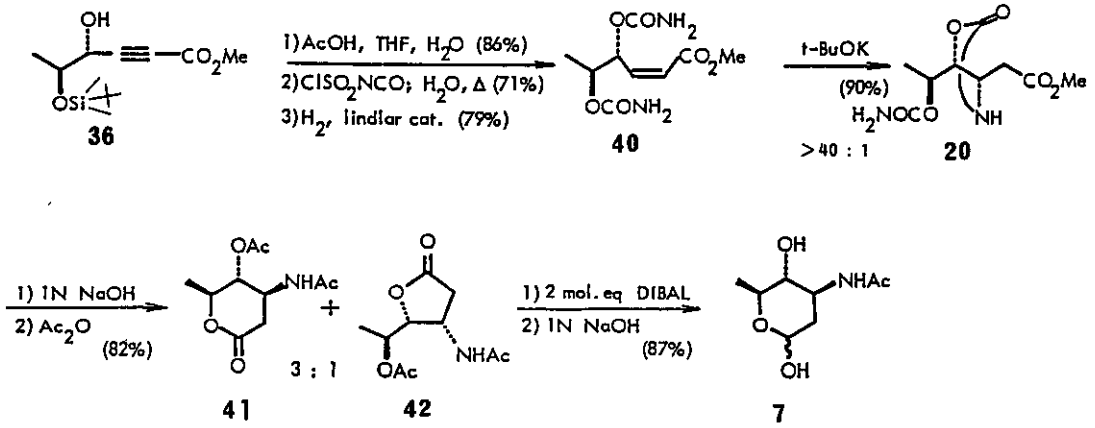


Figure 18

activity.[31] Our synthesis started from the erythro-diol derivative **36** (Figure 18),[8] which was prepared by the coupling of lithium acetylide of methyl propiolate with **35**. Attempts to improve the Cram selectivity (5:1) by changing the protecting group and metal ion were unsuccessful. The silyl ether **36** was converted to the key intermediate **40**, which was cyclized regio- and stereoselectively under the standard conditions to afford the trans-oxazolidinone (1,2-syn) **20** in a ratio of >40:1, apparently higher than the E series **15**.[5] Alkaline hydrolysis of both the carbamate and ester groups, evaporation of the volatiles, and lactonization with acetic

anhydride were performed in one pot to give a 3:1 mixture of δ- (41) and γ-lactones (42). The combined lactone mixture was reduced with 2 molar equiv. of DIBAL at low temperature to give the acetylated pyranose. Attempted direct removal of O-acetyl group by using excess DIBAL failed because of the concomitant reduction of hemiacetal. Alkaline hydrolysis of the remaining acetoxy group afforded the desired L-N-acetylacosamine (7).[8]

9. Synthesis of L-N-Benzoylristosamine

Ristosamine (4) is another naturally occurring isomer, isolated as a carbohydrate constituent of vancomycin group antibiotics such as ristomycin.[1,30] Our synthesis of L-N-benzoylristosamine **8** was outlined in Figure 19.[8] The key intermediate **34** was prepared from **36** in 5 steps, which cyclized to the desired 1,3-syn (1,2-anti) product **28e** exclusively as discussed above. Subsequent hydrolysis and benzoylation resulted in the formation of the known γ-lactone **43**, which was then reduced to give L-N-benzoylristosamine **8**.[8]

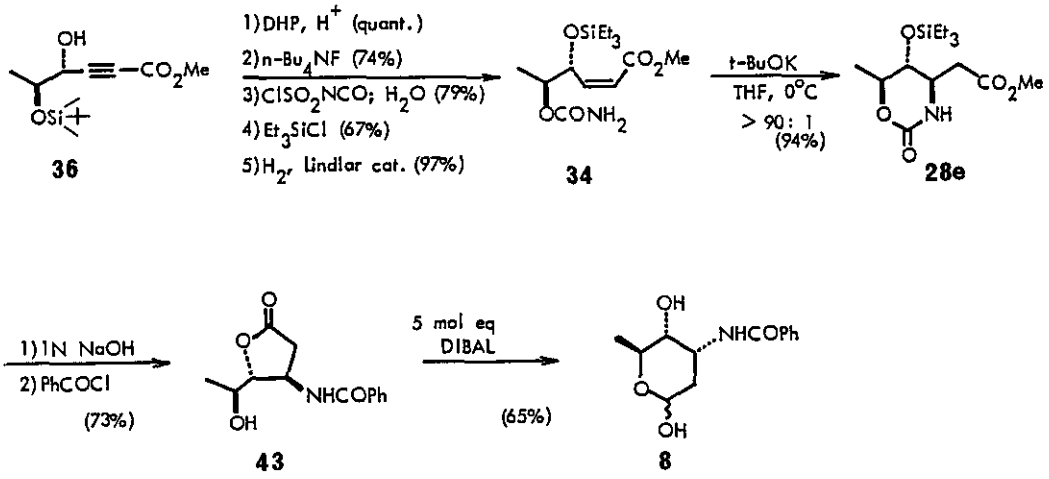
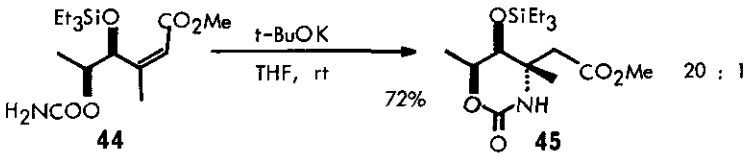


Figure 19

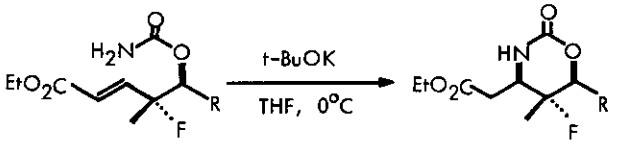
10. Related Conjugate Addition Reactions

The intramolecular conjugate addition of δ-carbamoyloxy- α, β-unsaturated ester 44 with an additional alkyl group at the β-position also proceeded under the standard conditions. However, the reaction was slow even at room temperature, and the diastereoselectivity was much lower (20:1) than that of **33**.[15] This may be accounted for by the *same transition state* model **J** with extra repulsion between the methyl group and C5-methyl.

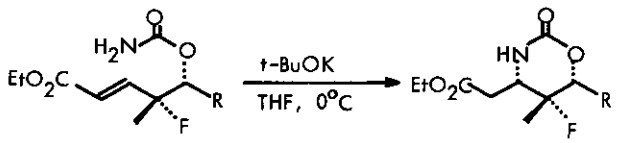


44 45

Recently, Kitazume et al. reported the related reactions of γ-fluoro-γ-methyl-δ-carbamoyloxy-α, β-unsaturated esters (**46**, **47**) with high 1,3-syn diastereoselectivity irrespective of the stereochemistry at γ position,[32] which is quite interesting in terms of γ-substituent effect (vide supra).

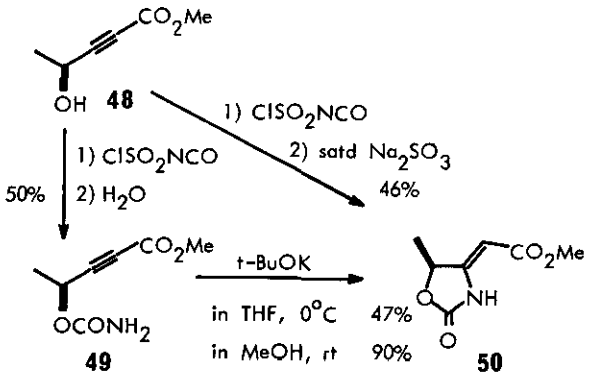


46 (R=Me, Ph)

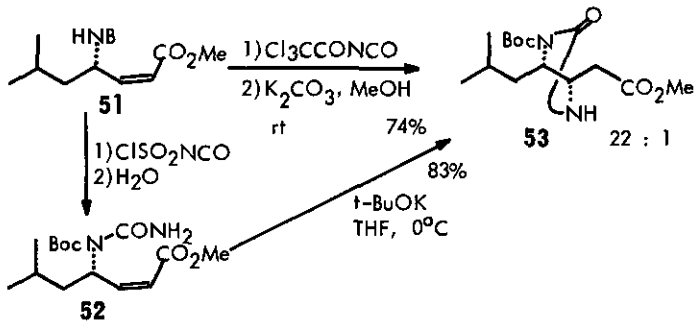


47 (R=Me, Ph)

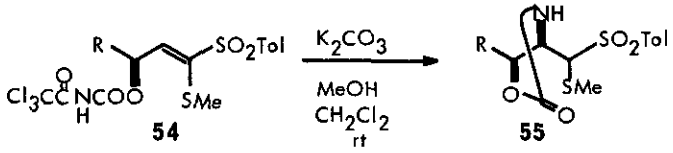
The conjugate addition of carbamate nitrogen to triple bond conjugated with ester occurred with t-BuOK in methanol in a better yield than in THF as exemplified by **49**. The reaction also proceeded from N-chlorosulfonylcarbamate, prepared in situ from from **48**, by treatment with saturated aqueous Na_2SO_3 solution.[15]



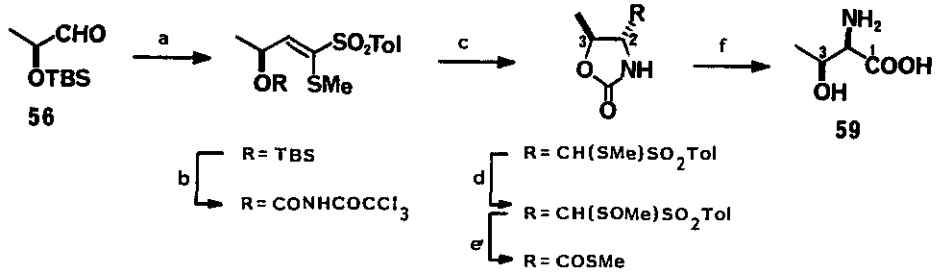
The urea derivative **52** underwent cyclization to give **53** under the standard conditions, and its N-trichloroacetyl derivative prepared from **51** also cyclizes under the basic hydrolytic conditions (K_2CO_3/MeOH).[15,33]



These conjugate additions have been further extended to the reactions of heteroolefins with electron drawing group.[10a] Cyclization of heteroolefins **54** with N-trichloroacetylcarbamate, prepared from nor-aldehyde and MT-sulfone,[34] occurred smoothly by treatment with K_2CO_3 in MeOH-CH_2Cl_2 to give 1,2-syn **55**. Its

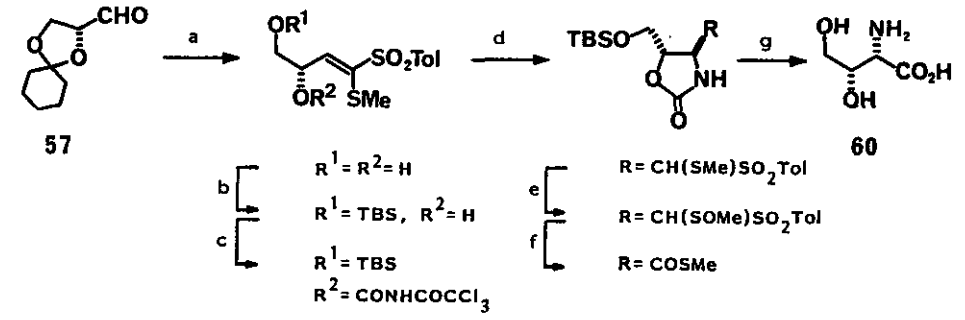


synthetic utility has been demonstrated by the stereoselective transformations of nor-aldehydes (**56**, **57** and **58**) to the corresponding syn-β-hydroxy-α-amino acids (**59**, **60** and **61**, respectively) (Figure 20-22).[10b]



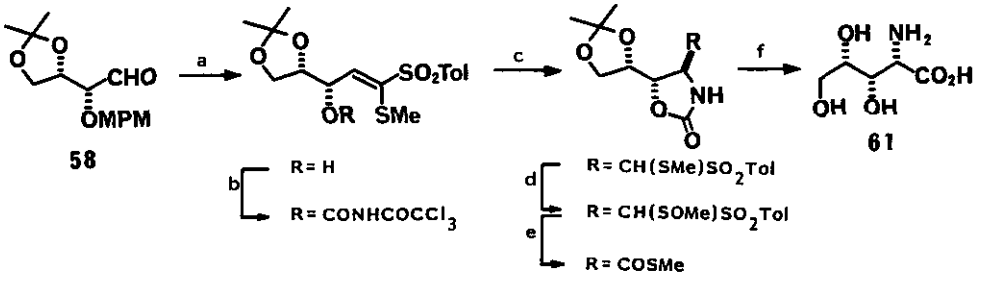
(a)[(i)$MeSCH_2SO_2Tol$, n-BuLi, THF, -78°C; (ii)MsCl, Py, 0°C→r t (70%). (b)[(i)1N-HCl, MeOH; (ii)CCl_3CONCO, CH_2Cl_2, 0°C. (c)K_2CO_3, MeOH-CH_2Cl_2(3:5), 2 h(86%). (d)MCPBA, CH_2Cl_2, 0°C(90%). (e)$(CF_3CO)_2O$(1.5 eq), Py(4 eq), CH_2Cl_2, -15°C, 6 h(87%). (f)[(i)K_2CO_3 (1.5 mol eq), H_2O-dioxane(1:1); (ii)6N-HCl, 110°C, 36 h(96%).

Figure 20



(a)(i)$MeSCH_2SO_2Tol$, n-BuLi, -78°C; (ii)MsCl, Py, NEt_3; (iii)p-TsOH, MeOH, reflux, 3 h(70%). (b)t-$BuMe_2SiCl$, DMAP, Py(99%). (c)CCl_3CONCO, CH_2Cl_2, 0°C. (d)K_2CO_3, MeOH-CH_2Cl_2(3:5), 4 h(98%). (e)MCPBA, CH_2Cl_2, 0°C, 2 h(81%). (f)$(CF_3CO)_2O$(4 eq), Py(10.5 eq), CH_2Cl_2, -15°C, 10 h(78%). (g)(i)K_2CO_3(1 mol eq), H_2O-dioxane(1:1); (ii)6N-HCl, 105°C(55%).

Figure 21

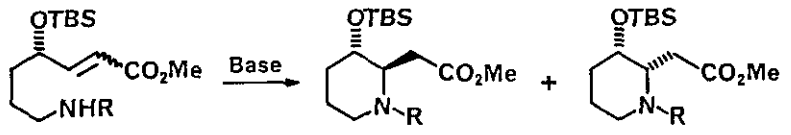


(a)(i)$MeSCH_2SO_2Tol$, n-BuLi, -78°C; (ii)MsCl, Py, NEt_3; (iii)DDQ, CH_2Cl_2, H_2O(57%). (b)CCl_3CONCO, CH_2Cl_2, 0°C. (c)K_2CO_3, MeOH, CH_2Cl_2, 4 h(73%). (d)MCPBA, CH_2Cl_2, 0°C(95%). (e)$(CF_3CO)_2O$(2 eq), Py(5 eq), CH_2Cl_2, -15°C, 17 h(73%). (f)(i)CF_3CO_2H-MeOH (1:1), 20 min; (ii)K_2CO_3(1.3 mol eq), H_2O, 4 h; (iii)1N-NaOH, 60°C, 4 h(55%).

Figure 22

In connection with the synthetic studies of piperidine and indolizidine alkaloids, we have investigated the related reactions of acyclic unsaturated amide derivatives **62**, and found reversal of their diastereofacial selection by the geometry of the double bond, in contrast to the carbamate series described before,[8] and its dependence on the nature of the nucleophile as summarized in Table 3.[11] The most remarkable feature is the formation of 1,2-syn products (**64**) from the E isomers. This may be best explained by the steric repulsion between the ester and acyl groups in **K(E)** (Fig. 23). These complementary and effective diastereoselection provides stereodivergent synthesis of 2,3-disubstituted piperidines.

Table 3



62 a, R = COOt-Bu
b, R = Ac
c, R = $COCF_3$
d, R = H

Substrate	Reaction *Conditions*[a]	Ratio 63 : 64	Yield % (63 + 64)
(Z)-62a	-50°C, 5 min	23 : 1	81
(E)-62a	-42°C, 5 min	1 :>60	81
(E)-62a	rt , 12 min	1 : 7	61
(Z)-62b	-36°C, 15 min	50 : 1	56
(E)-62b	-48°C, 15 min	1 : 7.4	68
(E)-62c	0°C, 1.5 h	--------	0
(E)-62c[b]	K_2CO_3,MeOH,rt,20 h	1.4 : 1	89 (R=H)

[a]Carried out in anhydrous THF with 0.8 equivalent t-BuOK, unless otherwise indicated.
[b]Reaction species should be free amine (E)-62d.

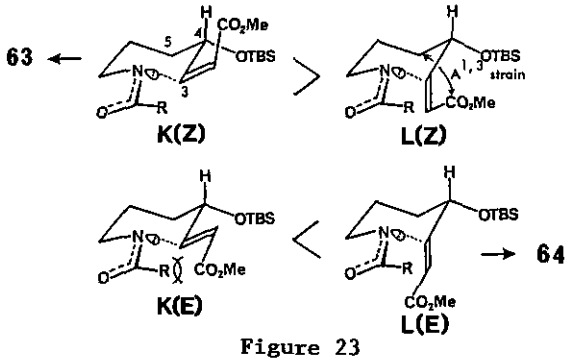
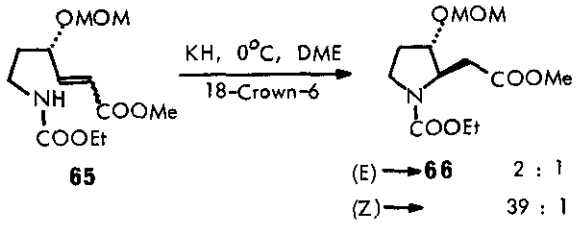
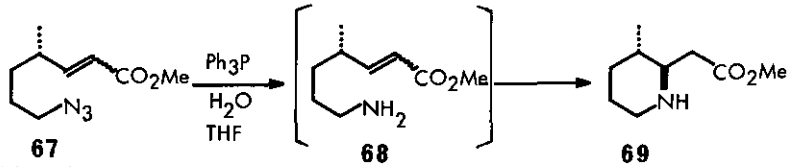


Figure 23

Fukumoto et al. reported the 1,2-anti preference in the cyclization of both isomers **65** to the same pyrrolidine **66**.[35] However, syn isomer is produced more from the E isomer than from the Z isomer also in this case.



On the other hand, the only 1,2-anti preference has been observed by Carrie et al.[36] in the cyclization of amine **68**, irrespective of double bond geometry. This is reasonable on our mechanistic consideration discussed above.



67 (E) : (Z) ≥ 95 : 5 or 67 : 33 **68** **69** 9 : 1

11. Conclusion

These base-catalyzed intramolecular conjugate additions of carbamate nitrogen to Michael acceptors have been shown to be a powerful tool for achieving diastereoselective syntheses of a variety of 1,2- and 1,3-amino alcohols including amino sugars, amino acids and alkaloids.

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