ChemComm
FEATURE ARTICLE

Stereocontrolled synthesis and reactivity of sugar acetylenes

Minoru Isobe,† Rena Nishizawa, Seijiro Hosokawa and Toshio Nishikawa

Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan. E-mail: isobem@agr.nagoya-u.ac.jp

Received (in Cambridge, UK) 29th June 1998, Accepted 17th August 1998

C-Glycosidation is of great significance in the organic synthesis of optically active materials, since it allows the introduction of carbon chains to sugar chirons and the use of sugar nuclei as a chiral pool as well as a carbon source. Silylacetylenes are sufficiently reactive to form 'sugar acetylenes' for the selective introduction of various acetylenic groups in an *alpha-axial* manner at the anomeric position of D-hexopyranose rings. 1,4-*Anti* induction, on the other hand, gives a different stereochemical outcome in the case of C-glycosidation of pentopyranose glycals. The mechanism of these reactions includes oxonium cation intermediates in which stereoelectronic and/or steric factors drive the direction of the incoming silylacetylene. Bis-C-glycosidation allows the introduction of sugars at both ends of some bis(trimethylsilyl)acetylenes. A 2,3-dideoxyglucose derivative provides the corresponding C-1 α-acetylenic compounds, which would increase the scope of C-glycosidation with silylacetylenes. In sugar acetylenes, the alkynyl group at the anomeric position of a pyranose ring is epimerized *via* a hexacarbonyldicobalt complex by treatment with trifluoromethanesulfonic acid. The three steps—cobalt complexation, acidic transformation and decomplexation—afford overall epimerization and thus one can obtain either the α- or β-alkynyl C-glycoside as desired. Ring opening of a dihydropyran derivative using Nicholas-type cation intermediates is also part of this study. Several sets of decomplexation conditions for *endo*-type acetylene–cobalt complexes provide various olefins possessing potential utility for synthesis. These methodologies have been utilized for the synthesis of polyoxygenated natural products and derivatives.

Introduction

In target-orientated synthesis, continuous efforts have provided organic chemistry with a considerable number of new synthetic methodologies. These include new concepts for multistep syntheses that achieve the desired target in a more straightforward manner. Syntheses of optically active natural products have posed many problems despite there being numerous methodologies available to the organic chemist. Sugars have been used as chirons as well as carbon sources in many organic syntheses.[1] The induction of one or more stereogenic centers onto a side chain extending from a sugar ring is another application which has attracted much attention.[2] We have designed and developed C-glycosidation (alkynylation) as a key reaction for the introduction of a carbon chain onto sugars. Those alkynylated compounds are called 'sugar acetylenes' for short,[3] and they have been applied to syntheses of natural products such as tautomycin[4] and ciguatoxin.[5]

Professor Minoru Isobe was born in Nagoya, educated in Nagoya and found his academic position in Nagoya University. He received his PhD degree with Professor Toshio Goto (silkworm diapause hormone) in 1973, and moved to Columbia University in New York as a postdoctoral researcher under the guidance of Professor Gilbert Stork (Prostaglandin F_2a). He was appointed an Associate Professor (1975–1991) in Professor Goto's group after Dr Yoshito Kishi left for Harvard University, and then Professor of Organic Chemistry (1991). His synthetic interests have mostly focused on the total synthesis of natural products, such as vernolepin, maytansine, okadaic acid, tautomycin and allo-yohimbane, and he is currently involved in the total synthesis of tetrodotoxin, ciguatoxin etc. *He has expanded his interests in bioorganic chemistry into the fields of bioluminescence, insect diapause, protein phosphatase inhibitors* etc. *and into those mechanistic elucidation processes including the counter proteins. He has received awards from the Agricultural Chemical Society for young chemists in 1980 and from the Society of Synthetic Organic Chemistry, Japan in 1996. He is currently a project leader at JSPS-RFTF.*

Rena Nishizawa was born in Osaka, Japan, in 1974. She received her BS degree from Nagoya University in 1997 and is currently an MS student under the supervision of Professor Minoru Isobe at the School of Bioagricultural Sciences of Nagoya University, involved in the study on the chemistry of C-glycosidation.

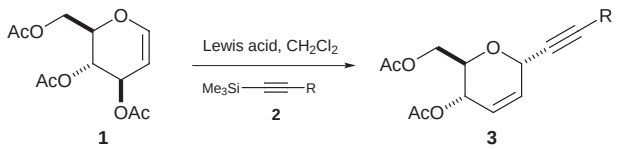
Dr Seijiro Hosokawa was born in Kurashiki, Japan, in 1968. He received his BS and MS degrees from Hokkaido University under the supervision of Professor Haruhisa Shirahama, and his PhD from Nagoya University under the supervision of Professor Minoru Isobe in 1996. After a year of postdoctoral research at Nagoya University and an additional one year at the Scripps Research Institute under the supervision of Professor K. C. Nicolaou, he became an Assistant Professor of Chemistry in 1998 in the Faculty of Pharmaceutical Sciences, Science University of Tokyo. His research interests include organic synthesis and bioorganic chemistry.

Dr Toshio Nishikawa was born in Nagano, Japan, in 1962. He received his BS degree in 1985 from Shizuoka University under the direction of Professor Daisuke Uemura and his MS degree in 1987 from Nagoya University. After spending time as a research associate at the research institute of the Sapporo Brewery Company (1987–1988), he returned to Nagoya University and received his PhD in 1995 from the same University under the supervision of Professor Minoru Isobe. Currently he is an Assistant Professor in the School of Bioagricultural Sciences at Nagoya University. His research interests include the development of new synthetic methods and the organic synthesis of nitrogen-containing natural products for the elucidation of biological problems.

C-Glycosidation with silylacetylene

During the course of our synthetic studies on okadaic acid,[6] an oxygenated marine natural product, we used the Hosomi–Sakurai reaction for the coupling of allyltrimethylsilane and tri-*O*-acetyl-D-glucal to prepare one of the starting materials.[7] We came across with a similar C-glycosidation under acidic conditions with silylacetylenes instead of allylsilane (R = $SiMe_3$).[8] The stereoselectivity of this reaction is excellent, giving only the α-acetylene, and is better than that in the allylsilane case (α:β = 96:4). C-Glycosidation with silylacetylenes allows a wide variety of substituents on the other end of the acetylene, and the resulting alkynylated sugar derivatives are of great potential utility as starting materials for natural product synthesis in optically active form.[9] Examples with different substituents are listed in Table 1.[8–10] In the reaction, R

Table 1 Alkynylation of tri-*O*-acetyl-D-glucal with silylacetylenes



Entry	R	Lewis acid	*T*/°C	Yield (%)
1	H	$TiCl_4$	0	0
2	Me	$SnCl_4$	−15	99
3	$SiMe_3$	$TiCl_4$	−20	75
4	$SiMe_3$	$SnCl_4$	−20	99
5	Bu^n	$TiCl_4$	−20	68
6	CH_2SPh	$TiCl_4$	−20	15
7	CH_2OAc	$TiCl_4$	−20	0
8	$(CH_2)_2OAc$	$TiCl_4$	−20	22
9	$(CH_2)_3OAc$	$TiCl_4$	−20	36
10	$(CH_2)_4OAc$	$TiCl_4$	−20	59

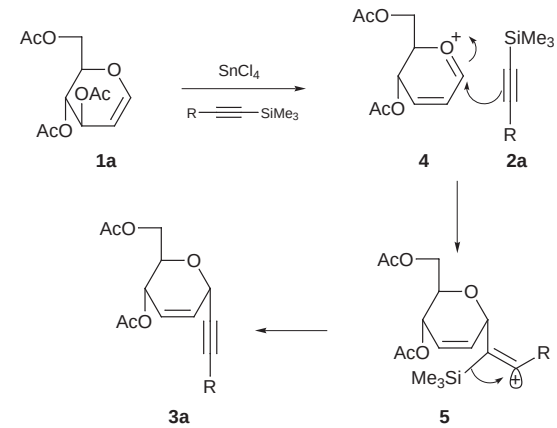
has to be larger than Me to afford alkynylation in reasonably good yield. The yield with R = H (entry 1) is almost 0%.[10a] On the other hand, the stronger Lewis acid $SnCl_4$ seems to work better than $TiCl_4$ in the case of R = $SiMe_3$ (entries 3 and 4). When R is a methylene group with an OAc moiety at the terminal position, *e.g.* the reaction with prop-2-ynyl acetate (entry 7), no alkynylated product is given. The yields of products increase with the higher homologous acetates (entry 8–10). This is due to the moderating effect of the methylene group(s) on the OAc moiety, which destabilizes the cationic transition state. These results suggest that the mechanism of this alkynylation reaction involves cationic charge development at the 2′-carbon in the transition state. In case of the phenylthio group (R = SPh, discussed later), the product is unstable with the stronger acids, and high yield is observed only with milder Lewis acid such as $BF_3{\cdot}OEt_2$; the nucleophilicity of (phenylthio)silylacetylene is high enough to yield the phenylthioethynylation product in good yield.[11]

Possible mechanism of C-glycosidation and proof of stereochemistry

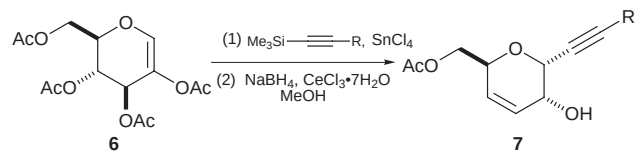
This C-glycosidation includes eliminative formation of the enonium ion (as shown in Scheme 1) to which silylacetylene can coordinate from the α side. The stereochemistry should largely be determined by the coordination between two π-electron orbitals of the onium and acetylene groups, while the stereoelectronic control allows the α-pseudo-axial orbital to make the bond, as shown in Fig. 1.

In 2,3,4,6-tetra-*O*-acetyl-D-glucal the C-glycosidation took place in a similar fashion to that in the tri-*O*-acetyl-D-glucal cases above with silylacetylenes (Scheme 2).[9] In this particular reaction, as shown in **8** and **9** (Scheme 3), the primary products are all unstable under the work-up conditions and/or silica gel chromatography. The reaction mixture is immediately subjected to hydride reduction ($NaBH_4$ and $CeCl_3$ in MeOH; or $LiAlH_4$, < −40 °C), in which the reagent accelerates elimination of the 4-OAc group (**8**) and then attacks the resultant ketone from opposite side of the *axially* oriented α-alkynyl group, thus giving a 2α-hydroxy group.

Incidentally, reduction with $LiAlH_4$ at higher temperature (*ca*. 0 to −10 °C) is usually followed by hydroalumination of the acetylene **8**, resulting in the formation of *trans* olefin **10**. The acetylene group in **3** can be partially reduced into *cis* olefin **11** with diimide (Fig. 2). These partial reduction products give NOEs in their NMR spectra between H-5 and H-1′ to prove the



Scheme 1



Scheme 2

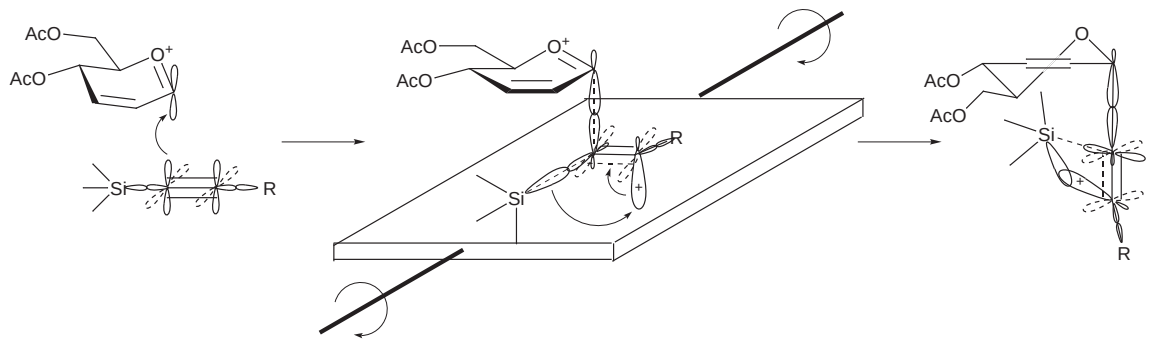
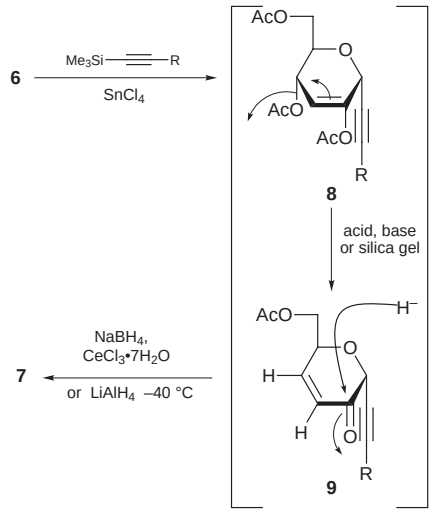


Fig. 1



Scheme 3

α stereochemistry of the original acetylene (Fig. 2).[9] Hydrosilylation of the benzylidene acetylene **21** (in Scheme 4) also gives two products (**12a** and **13a**), providing further evidence for the stereochemistry; thus, similar NOEs are observed. These benzylidene compounds have the bulky olefinic group in the α axial position in **12** or the α equatorial position in **13**, the latter showing an NOE between H-1 and H-4 due to the boat conformation of the tetrahydropyran ring.

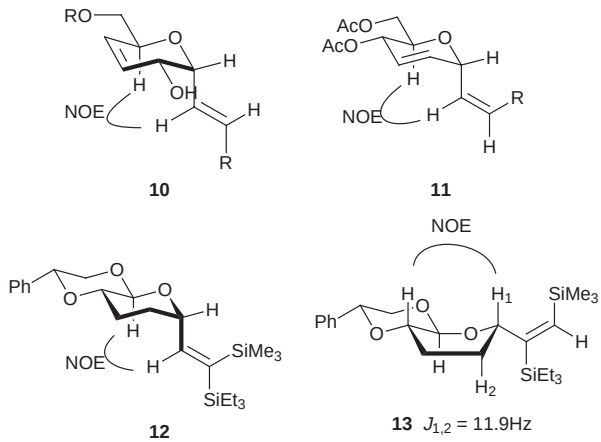
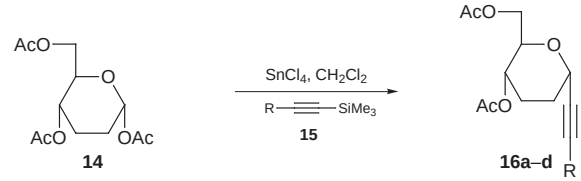


Fig. 2

Expansion of C-glycosidation to similar systems

In Table 2 other examples of C-glycosidation of 2,3-dideoxyglucose derivative **14** with silylacetylene are shown. The acetylation of the glycoside is critical to provide the C-1 leaving group which generates the oxonium ion, with which silyl acetylenes can react to form the α sugar acetylene. Scheme 4 illustrates the preparation of these compounds in order to prove the stereochemistry, and includes C-glycosidation of the saturated pyran ring. In this case the C-1 OAc group in **14** is necessary to provide a good leaving group, to generate the oxonium cation **17** to which the silylacetylene coordinates. After conversion to the corresponding 4,6-benzylidene derivative **21**, its acetylene group was subjected to hydrosilylation to provide a mixture of regioisomers **12a** and **13a**.[12]

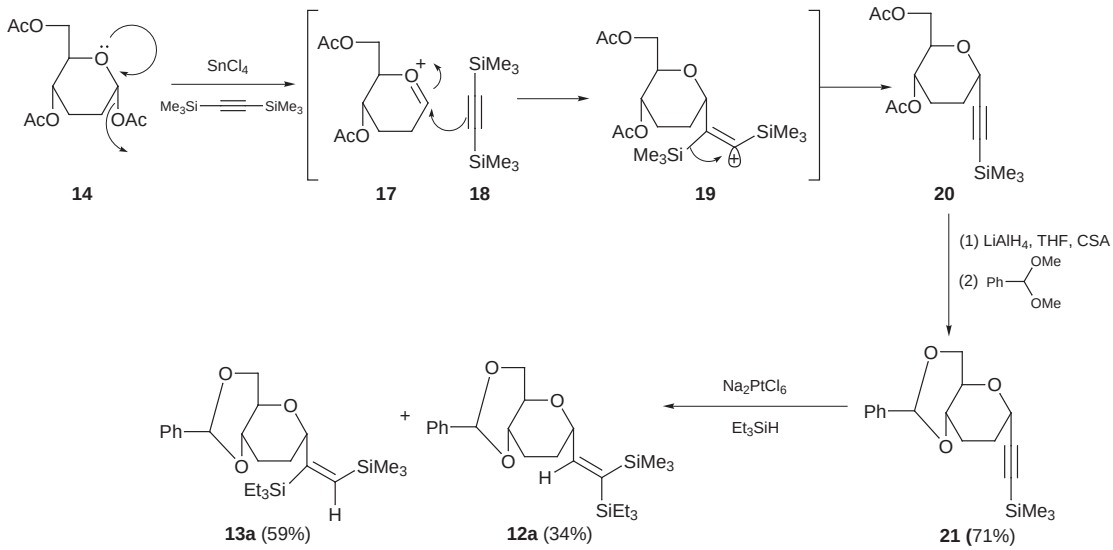
Table 2 C-glycosidation of 2,3-dideoxyglucose derivative **14** with silylacetylene **15**



Entry	Alkyne	R	*T*/°C	Product	Yield (%)
1	**15a**	$SiMe_3$	0	**16a**	73
2	**15b**	$C{\equiv}CSiMe_3$	0	**16b**	71
3	**15c**	(*Z*)-CH=CHCl	0	**16c**	83
4	**15d**	(*Z*)-CH=CHC≡$CSiMe_3$	−78	**16d**	35

Sugars at both ends of an acetylene

In the C-glycosidation of silylacetylenes with glucal type compounds, both of the examples in Schemes 1 and 2 afford different sugar products (R = $SiMe_3$) bearing trimethylsilylacetylene moieties, respectively. But these silylacetylenes do not react further with another equivalent of glycal. This lack of reactivity is observed for prop-2-ynyl acetate (entry 7, Table 1); thus no double C-glycosidation product was obtained in this particular case, presumably due to the presence of an electron-



Scheme 4

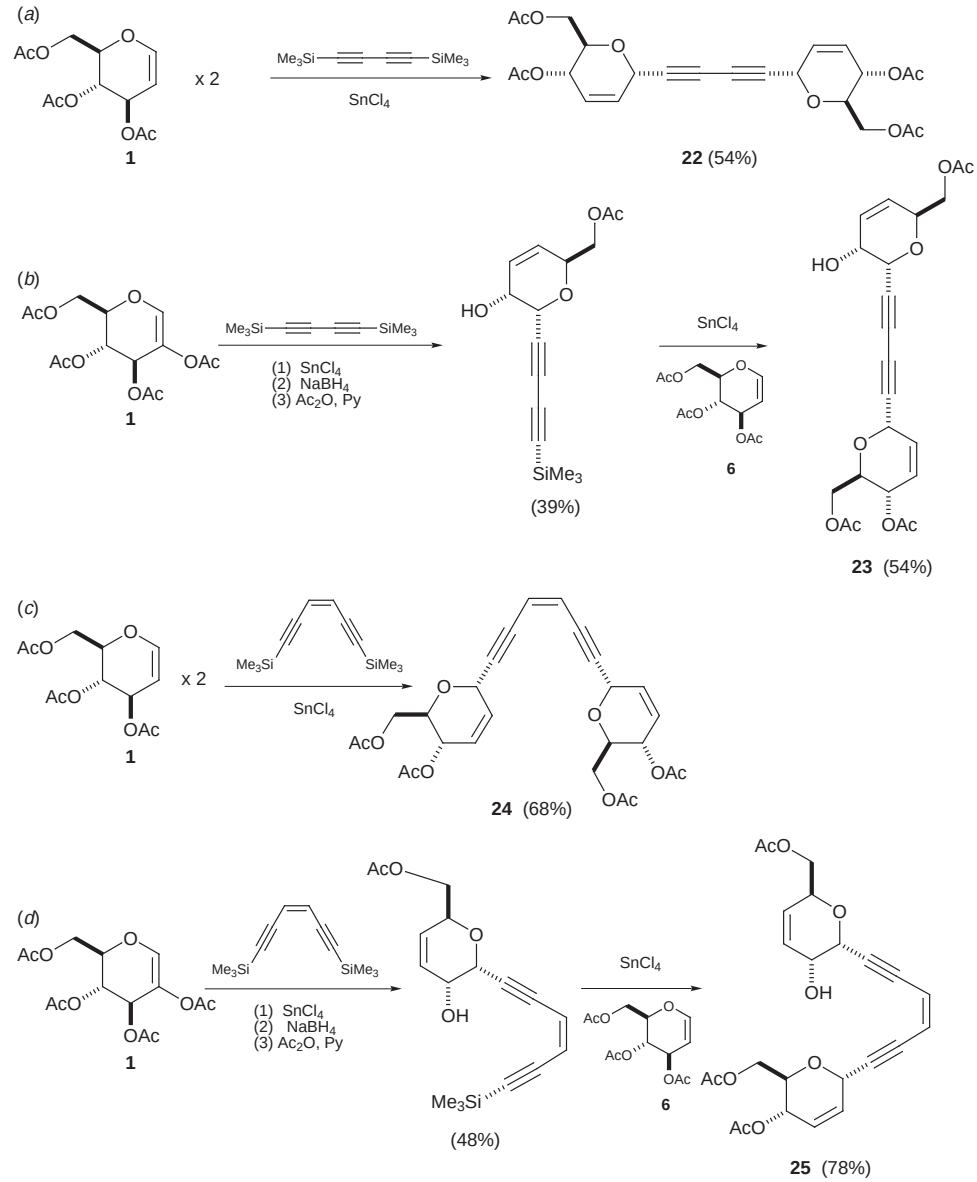
withdrawing oxygen atom at the properglic position, that destabilizes the cationic intermediates. However, further examination of some other reactions provided several good examples of double C-glycosidation between two glycals and bis(silylacetylene)s connected by longer carbon chains. Scheme 5(*a*) and (*b*) show the first examples of disilylacetylenes with sugar rings to both ends. The reaction process is stepwise, providing first mono- and then di-glycosidation products. This fact suggests that the second C-glycosidation is slower than the first,[13] and that it is possible to attach two different kinds of sugar ring, as in Scheme 5(*b*) and (*d*). The silylacetylene moieties can also form the ends of endiyne compounds [Scheme 5(*c*) and (*d*)].

Phenylthioacetylenes

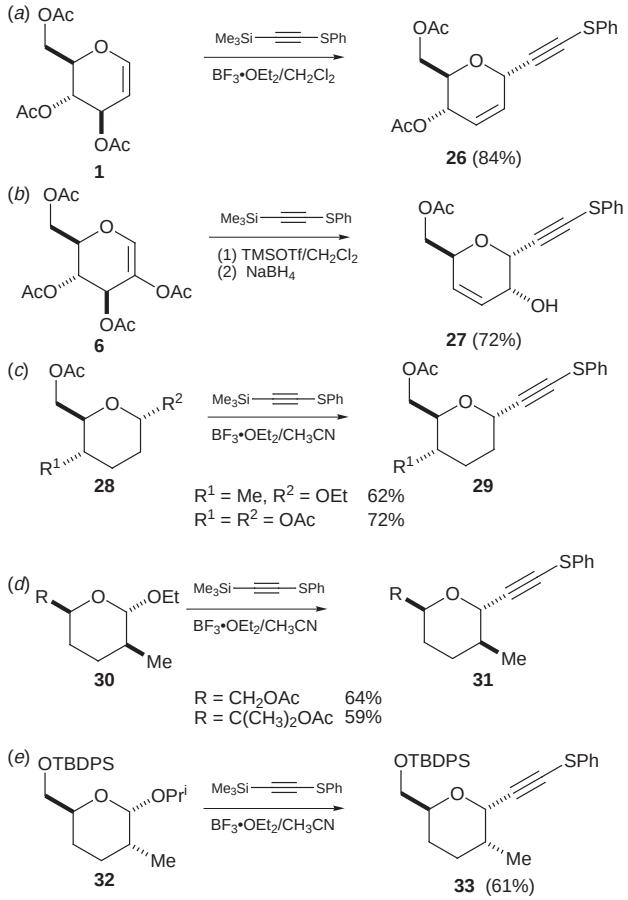
Higher reactivity is observed for silylacetylenes carrying a phenylthio group at the other end. The reagent 1-trimethylsilyl-2-phenylthioacetylene is prepared from the lithium salt of ethynyltrimethylsilane and *S*-phenyl benzenethiosulfonate.[14] In this case high yields are obtained with a weaker Lewis acid catalyst such as $BF_3{\cdot}OEt_2$ by stirring for 20 min in MeCN. In Scheme 6(*a*) and (*b*)[12,15] are demonstrated the first two examples, with quantitative formation of the phenylthioacetylenes. Similar C-glycosidations are possible from *O*-glycosides [Scheme 6(*c*)–(*e*)].[4b,15,16] Most of these examples give high yields with 1-trimethylsilyl-2-phenylthioacetylene in the presence of $BF_3{\cdot}OEt_2$. Mechanistically, the phenylthio group can provide electrons which help develope cationic charge at the adjacent carbon in the transition state of the C-glycosidation. The product, a phenylthioacetylenic sugar, does not react further with $BF_3{\cdot}OEt_2$, but does with $SnCl_4$. The yields dramatically drop with stronger Lewis acid catalyst (such as $SnCl_4$ or $TiCl_4$) and/or by prolonging the reaction period.

Other interesting examples

Nicolaou *et al*. reported a similar example of silylacetylene addition to methylated glucal acetate [**34** in Scheme 7(*a*)].[17] Williams demonstrated that bromide (in **36** and **38**) is a better leaving group, using an alkynyltin species and zinc chloride as the Lewis acid catalyst [Scheme 7(*b*) and (*c*)].[18] They reported high α selectivity with hexose (**37**), but variable selectivity with pentofuranose (**39**). Recently Veyrieres described the reaction of 2-deoxy-2-azido-1-bromo compound **40** with an alkynyltin species in the presence of silver tetrafluoroborate catalyst [Scheme 7(*d*)].[19] Martin found that the selectivity of the



Scheme 5

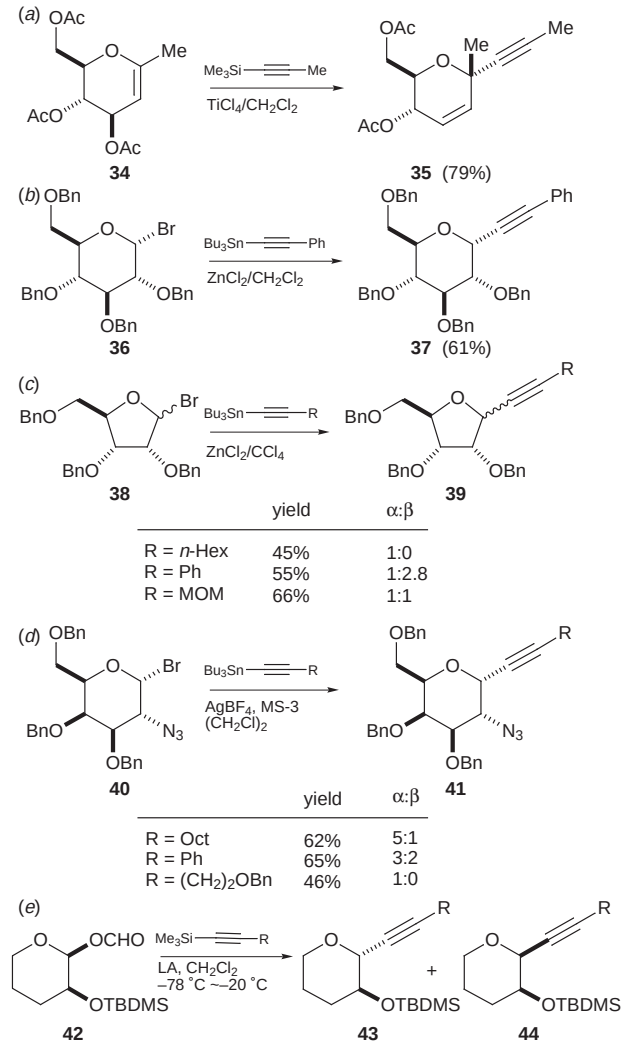


Scheme 6

reaction of (±)-1-formyl-2-alkoxypentopyranose with various silylacetylenes varied with the substituent on the other end of the acetylene moiety; thus, 1,2-*syn* and 1,2-*anti* selectivities were observed as shown in Scheme 7(*e*).[20]

1,4-*anti* Selectivity of silylacetylene to pentopyranoside

We expanded the *C*-glycosidation reaction to pentopyranose derivatives such as di-*O*-acetyl-D-xylal **45** and di-*O*-acetyl-L-arabinal **47** during the course of synthetic studies on the ABC segment of ciguatoxin (CTX, see compounds **109**–**111**), a polyether marine natural product.[21] This glycosidation provides a single stereoisomer.[22] During the CTX synthesis, this stereogenic center is destroyed and is thus not significant in the above mentioned synthesis (we did not even determine whether the stereochemistry was α or β at first). Recently, the stereochemical induction turned out to be in striking contrast to the previous cases. Namely, tri-*O*-acetyl-D-glucal **1** and bis-trimethylsilylacetylene react in the presence of a Lewis acid in a highly stereospecific manner to give exclusively the α-axial orientation in the product **3**.[9] The examples of silylacetylene addition to hexopyranoglycals occur under various acidic conditions but they all produce only the α-acetylene products with 1,4-*syn* selectivities higher than 95%. On the other hand, similar addition of silylacetylene to pentopyranoglycal diacetates (such as **45** and **47**) and dipivalates (**51** and **56**) affords the opposite results; thus, 1,4-*anti* stereochemistry is observed with the exclusive products **46**, **48**, **49**, **50**, **53**, **55**, **57** and **58** in the pentopyranose cases as shown in Table 3. Various nucleophiles add to the same pentopyranose glycals to afford similar results.[23]



	LA	yield (%)	**43** : **44**
R = H	$TiCl_4$	60	0 : 100
R = H	$SnCl_4$	73	0 : 100
R = $SiMe_3$	$TiCl_4$	74	66 : 34
R = $SiMe_3$	$SnCl_4$	68	80 : 20
R = Me	$TiCl_4$	81	70 : 30
R = Me	$SnCl_4$	67	100 : 0
R = Pr	$TiCl_4$	66	80 : 20
R = Pr	$SnCl_4$	72	90 : 10
R = Ph	$TiCl_4$	64	80 : 20
R = Ph	$SnCl_4$	71	95 : 5

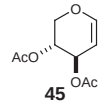
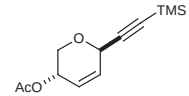
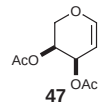
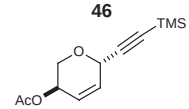
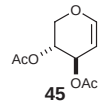
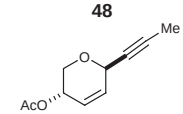
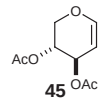
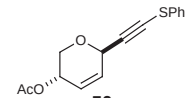
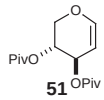
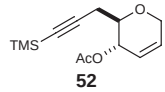
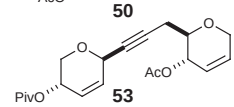
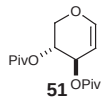
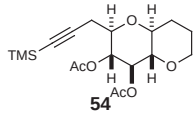
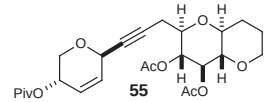
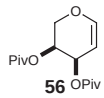
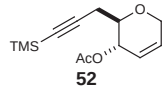
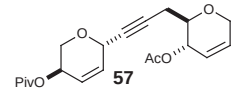
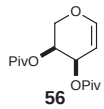
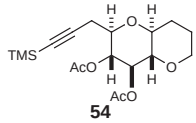
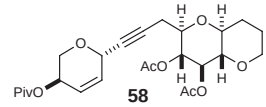
Scheme 7

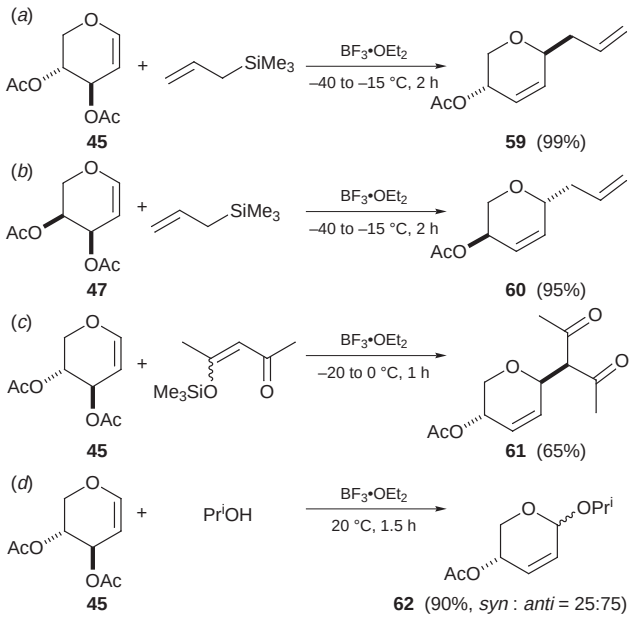
Application of the Hosomi–Sakurai reaction to this system provides the 1,4-*anti* products [Scheme 8(*a*) and (*b*)]. The reaction of a vinylsilyl ether with **45** also affords a 1,4-*anti* product **61** [Scheme 8(*c*)]. An oxygen nucleophile (propan-2-ol) mainly yields a 1,4-*anti* product, although the *syn*:*anti* selectivity was 25:75 [Scheme 8(*d*)].[23]

Stereochemical control

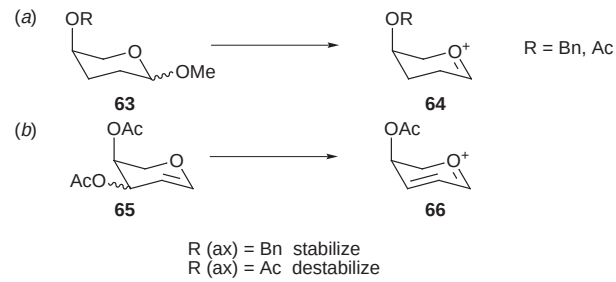
Miljkovic *et al*. reported a 1,4-position stabilization effect for the oxocarbenium intermediate in a hydrolysis of pentopyranoside[24] [Scheme 9(*a*)]; thus, the benzyloxy group of **63** (R = Bn) sits in an axial orientation [**64**(**4*ax***) in Fig. 3] to stabilize the oxocarbenium ion through space rather than in an equatorial position **64**(**4*eq***). On the other hand, an acyloxy group such as an acetyl group provided no stabilizing or even destabilizing

Table 3 1,4-*anti* Selecvtivity in the reaction of silylacetylene with pentopyranoside

Entry	Glycal	Nucleophile	Lewis acid (conditions)	Major product	Yield (%)
1	 **45**		$TiCl_4$ –40 ~ –15 °C 2 h	 **46**	73
2	 **47**		$TiCl_4$ –40 ~ –15 °C 2 h	 **48**	97
3	 **45**		$TiCl_4$ –40 ~ –15 °C 2 h	 **49**	99
4	 **45**		$BF_3{\bullet}OEt_2$ 0 °C 15 min	 **50**	88
5	 **51**	 **52**	$TiCl_4$ –20 °C 2 h	 **53**	87
6	 **51**	 **54**	$SnCl_4$ –20 °C 40 min	 **55**	96
7	 **56**	 **52**	$TiCl_4$ –20 °C 2 h	 **57**	54
8	 **56**	 **54**	$SnCl_4$ –20 °C 2 h	 **58**	83



Scheme 8



Scheme 9

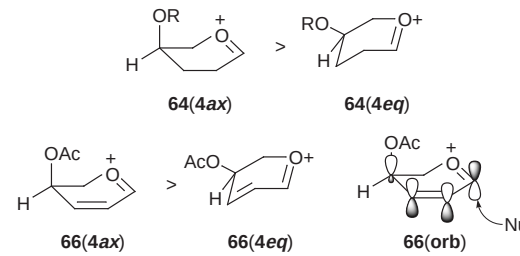
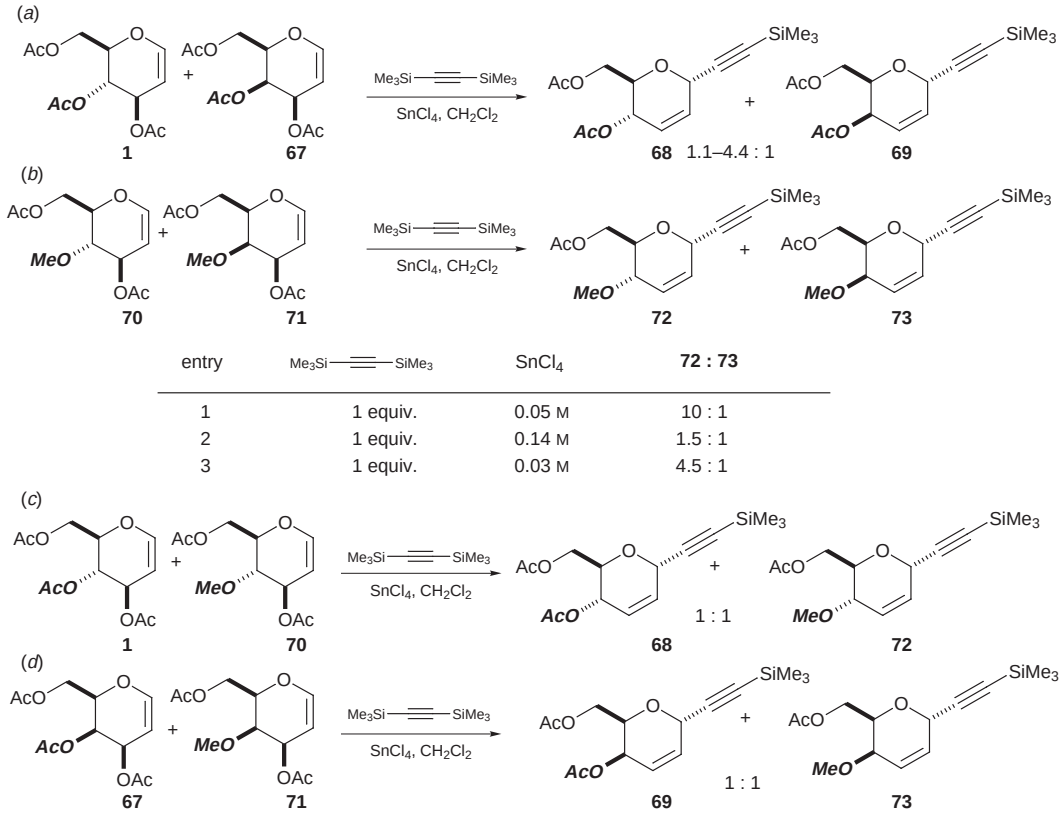


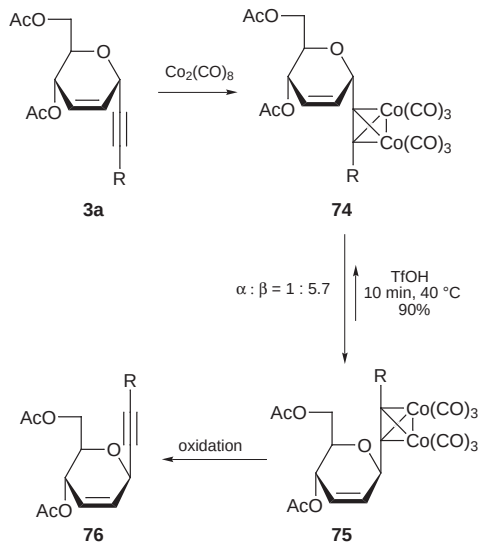
Fig. 3

effect during the hydrolysis. A similar explanation might be possible in the enoxocarbenium ion **66** formed during pentose C-glycosidation [Scheme 9(*b*)]. The suggestion that the reaction proceeds *via* **66**(**4*ax***) and not **66**(**4*eq***) would explain the 1,4-*anti* orientation, because the nucleophile silylacetylene would approach from the α side (*anti* to the acetoxy group). An alternative explanation may be due to orbital interaction; thus, the axially orientated 4β-acetoxy group reduces the electron density in the π-electron lobe at C-2 in the β-face, making the *anti*-lobe at C-1 more reactive [**66**(**orb**)]. We must await further experimental results before deciding which mechanism is operative.

These results prompted us to do mixing experiments with glucal and galactal derivatives (Scheme 10) in our laboratory to



Scheme 10



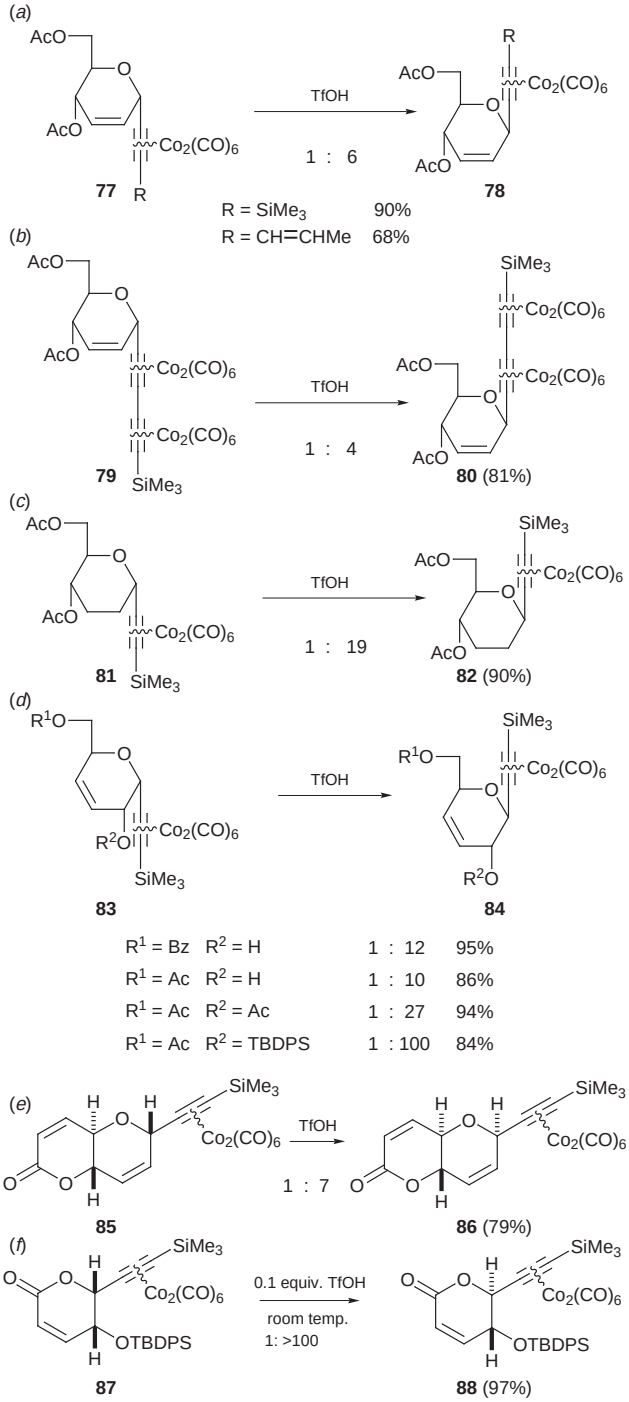
Scheme 11

determine the relative rates of C-glycosidation in pentopyranose systems, to thus avoid conformational problems. Glucals always give higher yields than galactals in C-glycosidations, even with the reaction being interrupted after only a short reaction time [Scheme 10(*a*) and (*b*)]. When mixtures of the 4-acetoxy and 4-methoxy substituted glucals or galactals were subjected to the C-glycosidation conditions [Scheme 10(*c*) and (*d*)], the ratio of the products was 1:1. These results for the bond formation process are striking different to those of the hydrolysis case, although similar oxocarbenium ions are involved. The mechanism and kinetics of these C-glycosidations need to be studied further.

Epimerization of the C-1 alkynyl group on the pyranose ring using an acetylenehexacarbonyldicobalt complex

The stereoselectivity of these C-glycosidations with silylacetylenes exclusively leads to products with the α-axial orientation. If an epimerization were possible which gave products with β orientation, this methodology would be more useful, giving access to both α and β configurations. Nicholas reported that complexation of an alkynyl group with octacarbonyldicobalt provides a hexacarbonyldicobalt complex which stabilizes the carbocation at the proparglic position.[25] Application of the Nicholas reaction to α-sugar acetylenes under acidic conditions would give the thermodynamically more stable β-equatorial isomer at equilibrium under the reaction conditions.[26] In fact the overall process including cobalt complexation, acid epimerization and oxidative decomplexation can take place as illustrated in Scheme 11. Reagents often used for the decomplexation include *N*-methylmorpholine *N*-oxide, cerium(IV) ammonium nitrate, ferric nitrate, iodine *etc*. Among these oxidants, iodine reacts very fast even at 0 °C to finish the reaction in 36 min, providing the acetylene in quantitative yield even with large excess of iodine. Often the last two steps can be carried out in one pot.

Examples of epimerization of the α sugar acetylenes into β ones are shown in Scheme 12(*a*) and (*b*), in which the 2,3-dehydro ring systems are involved with different acetylene cobalt complexes. The ratios of equilibration in these cases are 1:4–6, rather low values which may be due to the single pairs of 1,3-diaxial interactions since they have an energy difference of only *ca*. 1 kcal mol^{-1}. The saturated ring system in Scheme 12(*c*) gives a higher ratio (1:19) due to three pairs of 1,3-diaxial interactions (Fig. 4). The ratios vary in Scheme 12(*d*) which includes 3,4-en-2-ol system; the ratios increase in accordance with the size of the alkoxy substituents. The major cause in this case may be due to 1,2-strain, as shown in Fig. 5.[26]



Scheme 12

Conformational preferences are not the only necessary factors for a high equilibrium ratio for the acetylene cobalt complex. The bicyclic example shown in Scheme 12(*e*) may have a rigid ring system, but the important thermodynamic factor is once again a single 1,3-diaxial interaction, resulting in a 1:7 ratio. Evidences of this 1,2-strain is clearly demonstrated in Scheme 12(*f*), where the ring system does not have the carbon corresponding to C-6. A Nicholas reaction makes the epimerization possible.[26]

Opening of the pyranose ring and re-cyclization

The above epimerization *via* the cation intermediate is an important characteristic of the cobalt complex in sugar acetylenes. The same cation intermediate is potentially applicable to medium ether ring formation and other useful protocols. Oxepane ring formation from six-membered ether precursors is usually impractical due to thermodynamic constraints. In Scheme 13, oxepene **89** is planned to cyclize from **92** *via* the cation **90** derived from the sugar acetylene hexacarbonyldicobalt complex **91**. The overall reaction is shown in Scheme 14; opening of the ring of the 3,4-unsaturated glucose derivative **83** takes place under acetolysis conditions (TfOH in Ac_2O at −40 °C) for a few hours to provide **93** as a diastereomeric mixture at the C-3 position. The *cis* olefinic compound **93** is decomplexed (**94**) and further manipulated *via* the protecting groups of the hydroxy moieties (**95**), cyclizing into the corresponding oxepene compound **96**. Decomplexation gives **97**, which has *syn-trans* stereochemistry.[27]

Ring opening also takes place with the 2,3-unsaturated system, as shown in Scheme 15. In this case, acid treatment of **98** generates the enoxocarbenium ion at the anomeric position (original sugar numbering C-1) and epimerization is followed by ring opening (**99**). The process is different from the above cases with 3,4-double bonds because the *cis*-2,3-unsaturated system has the cation at the allylic position, which can equilibrate into the more stable *trans* allylic cation, resulting in the acetylation of the 7-hydroxy group. If this occurs, one can make produce a spontaneous ring-recyclization by positioning a nucleophilic hydroxy group at the other side of the acetylene hexacarbonyldicobalt group.

Scheme 16 illustrates this plan; the substrate, unsaturated six-membered **101**, should transform into **104** *via* the cation intermediates **102**, in which the *cis* allylic cation at the C-1 position can equilibrate to the more stable *trans* allylic cation **103**. The latter cannot re-cyclize back to **101** and waits for the addition of the hydroxy group on the other side to afford **104** with various ring sizes, such as seven-, eight-, nine- and ten-membered rings, depending upon the number of methylenes.

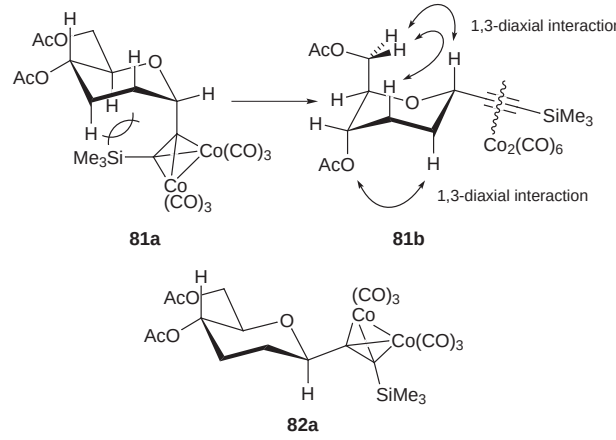


Fig. 4

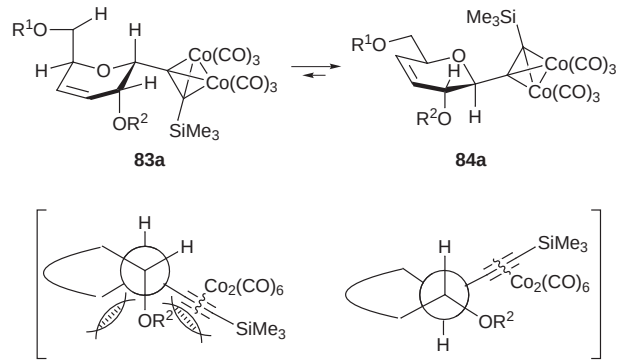
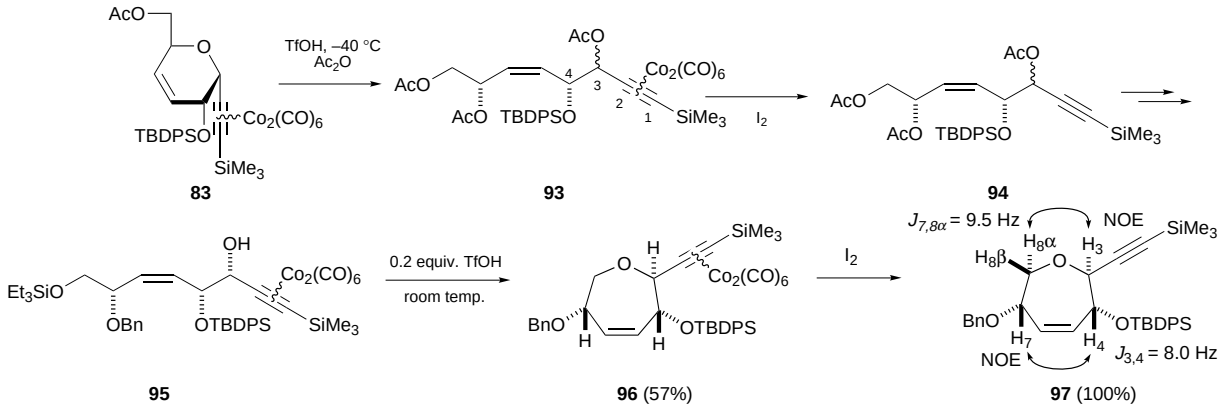


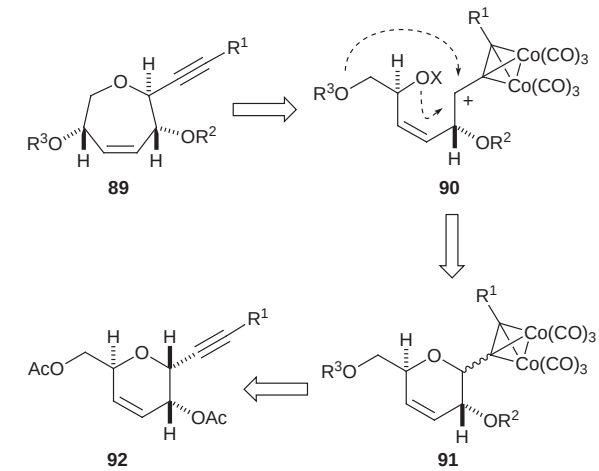
Fig. 5



83 **93** **94**

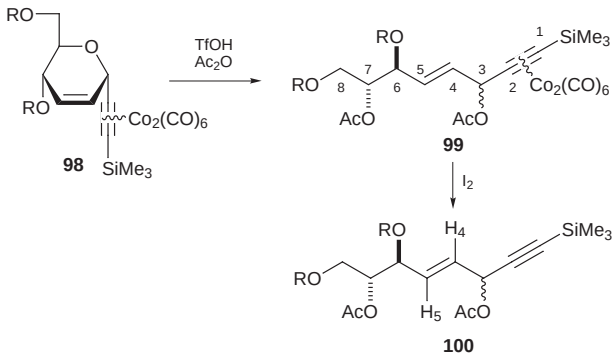
95 **96** (57%) **97** (100%)

Scheme 14



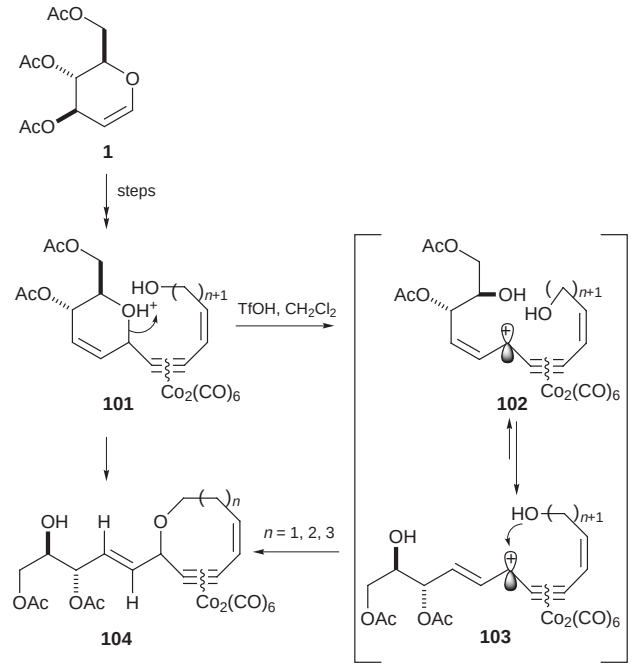
89 **90** **92** **91**

Scheme 13



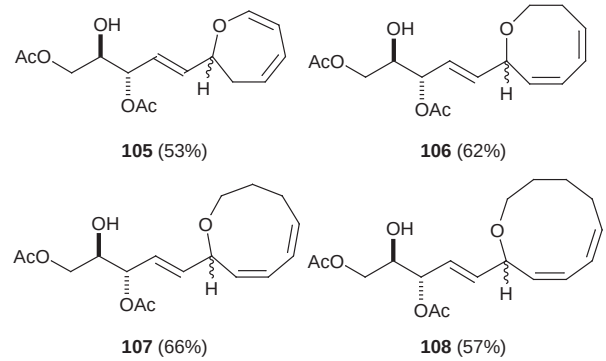
98 **99** **100**

Scheme 15



1 **101** **102** **104** **103**

Scheme 16



105 (53%) **106** (62%)

107 (66%) **108** (57%)

The multistep sequence of reactions (**1**→**101**) includes C-glycosidation with silylacetylene, and Pd-catalyzed ene–yne coupling with the *cis* vinyl iodide to provide the precursor **101**.[5]

The resulting ring compounds (**104**) are a new type of acetylene cobalt complex with the complex inside the ring system; thus, the *endo*-complex cannot be decomplexed under oxidative conditions as for the *exo*-complex. Finally, Rh-C was found to be effective for the synthesis of the decomplexed dienes **105**–**108** under high pressure H_2.[5] The carbons corresponding to the original acetylene complex end up as the olefinic carbons (except for the double bond transposition in the seven-membered system). Incidentally, the rhodium catalyst thus formed during the decomplexation of hexacarbonyldicobalt fulfils the reductive function of the cobalt complex into olefins, but did not reduce the double bonds under the reaction conditions.

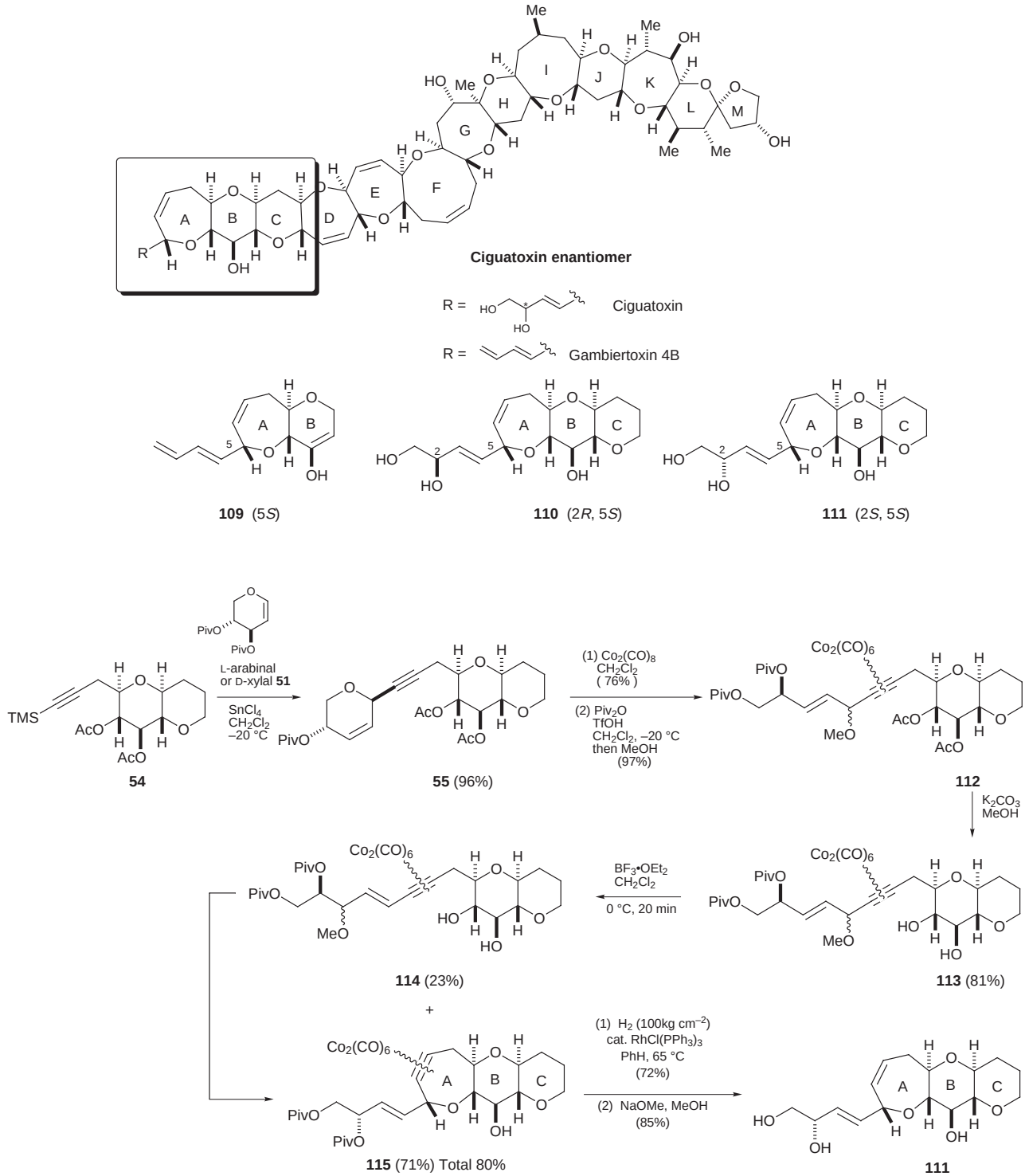
Application to ciguatoxin synthesis

Above methodologies have been developed for application to the synthesis of ciguatoxin and gambiertoxins, potent toxins causing marine ciguatera poisoning. When this synthesis was started, the absolute configuration and part of the relative

configuration had not been determined. Recently, Yasumoto reported that the absolute configuration of ciguatoxin is that of the opposite enantiomer.[21] Various side chains are attached to the 5 position of the A-ring, such as a 1,3-diene or 1-en-3,4-diol. We have demonstrated the synthesis of the AB(C) ring system with three possible side chains (**109**–**111**).[23] The synthesis of one of these compounds is shown in Scheme 17. The silylacetylene moiety was attached to the bicyclic compound **54**, which added to D-xylal **51** to afford the coupling product *anti*-acetylene as a single stereoisomer **55**. The cobalt complex of **55** was treated with pivalic anhydride in the presence of TfOH to afford the *trans* olefin (**112**). This was followed by hydrolysis of the acetate protecting group to give the hydroxy group (**113**) and then by a second treatment with acid to provide the tricyclic compound (**115**) together with some isomeric compound (**114**). Decomplexation of the *endo*-cobalt complex was achieved to give **111** using Wilkinson's catalyst under the high pressure hydrogen atmosphere.[5,23]

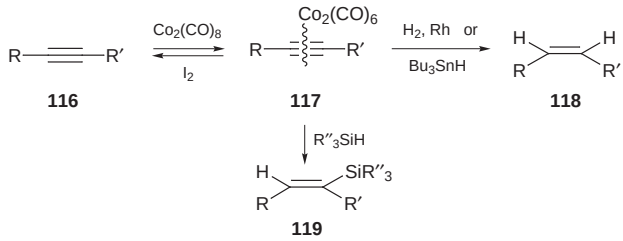
Novel reductive decomplexation of acetylene hexacarbonyldicobalt complex

Acetylene hexacarbonyldicobalt complexes[28] have mostly been used for the protection of triple bonds as well as for C–C bond



Scheme 17

and C–O bond formation reactions,[23,29] and thus they have been applied to natural product syntheses.[30] The most common decomplexation is an oxidative procedure leading to the original triple bond, but this is limited to the exocyclic cases as discussed previously. In endocyclic complexes only decomplexation under high pressure hydrogen using a Rh catalyst provides olefinic cyclic ethers.[5,23] Recently Kuwajima reported a Birch reduction for such decomplexation.[31] Here we describe two additional decomplexation protocols applicable to either *exo*- or *endo*-cyclic acetylene cobalt complexes, as shown in Scheme 18.[32]



116 **117** **118** **119**

Scheme 18

The new method is applicable to either *endo*- or *exo*-complexes to provide simple *cis*-olefins (with tri-*n*-butyltin hydride) or *cis*-vinyl silanes (with trialkylsilanes or triarylsilanes) at the original position of the acetylene (Scheme 18). Various examples using SnH are shown in Table 4. A simple terminal acetylene–dicobalt complex is converted to a terminal olefin (entry 1). Two examples of *exo*-complexes gave *cis*-olefins (entries 2 and 3). *endo*-Complexes of seven- and nine-membered rings are also shown (entries 4–7). Of particular interest is the bis(hexacarbonyldicobalt) complex of the nine-membered ring, which is only able to decomplex under these conditions, since using rhodium under high pressure conditions failed to give the diene.[32] This method was applied to the synthesis of ABC fragment **109** of gambiertoxin.[33]

Table 4 Decomplexation of acetylene hexacarbonyldicobalt with Bu^n_3SnH

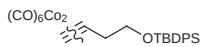
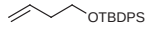
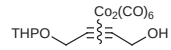
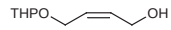
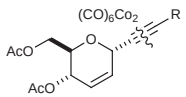
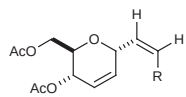
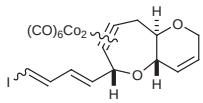
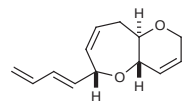
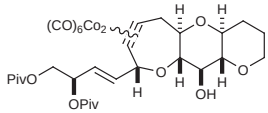
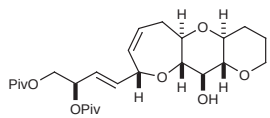
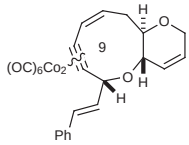
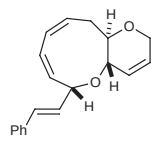
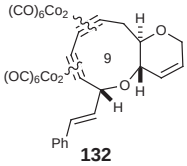
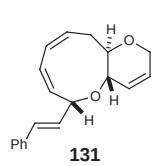
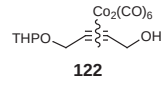
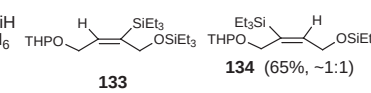
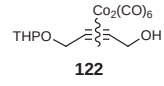
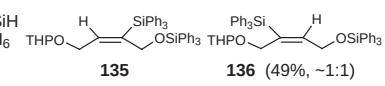
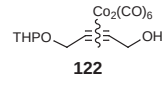
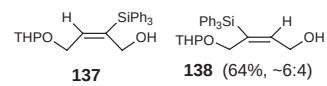
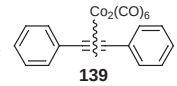
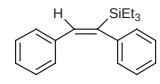
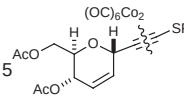
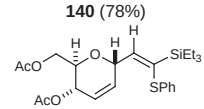
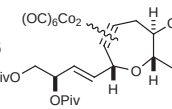
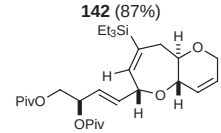
Entry	Substrate	Product	Yield (%)
1	 **120**	 **121**	60
2	 **122**	 **123**	64
3	 **124** R = H **74** R = $SiMe_3$	 **125** **11**	55 64
4	 **127**	 **128**	81
5	 **129**	 **110**	82
6	 **130**	 **131**	61
7	 **132**	 **131**	35

Table 5 Decomplexation of acetylene hexacarbonyldicobalt with R_3SiH

Entry	Substrate	Silane/solvent	Product (% yield, ratio)
1	 **122**	Et_3SiH C_6H_6	 **133** **134** (65%, ~1:1)
2	 **122**	Ph_3SiH C_6H_6	 **135** **136** (49%, ~1:1)
3	 **122**	Ph_3SiH C_6H_6–EtOH	 **137** **138** (64%, ~6:4)
4	 **139**	Et_3SiH C_6H_6	 **140** (78%)
5	 **141**	Et_3SiH C_6H_6	 **142** (87%)
6	 **143**	Et_3SiH C_6H_6	 **144** (74%)

Similarly the acetylene hexacarbonyldicobalt *endo* or *exo* complexes can be converted into the corresponding *cis*-vinylsilanes. In entries 1 and 2 in Table 5, alcohol (**122**) is converted using triethyl- or triphenyl-silanes into *cis*-vinylsilanes as the silyl ethers. When this reaction is carried out in EtOH–benzene, the corresponding alcohols (**137**, **138**) are obtained in free form. A symmetric precursor (**139**) affords a single product (**140**). A sterically unequal acetylene **141** is converted into a single hydrosilation product (**142**). The *endo* complex **143** also gives a single product (**144**) in which the silyl group is situated away from the neighboring substituent. Thus, the hydrosilylation of cobalt complexes becomes synthetically very useful.

Summary

This review describes new aspects of sugar acetylenes, including their preparation (C-glycosidation with silylacetylene), epimerization and medium ring re-cyclization *via* acetylene hexacarbonyldicobalt complexes. Expansion of these synthetic concepts demonstrates some applicability to the synthesis of ciguatoxin. New reactions have been developed for decomplexation of the cobalt acetylene complexes, particularly for both the *endo*- and *exo*-complexes. This chemistry will further develop towards better synthetic methods for natural product synthesis.

Acknowledgments

This review is a summary of recent studies largely achieved in our laboratory. The authors are gratefully indebted to Dr Yoshiyasu Ichikawa, Mr Takahiro Tsukiyama, Dr Shigeyoshi Tanaka, Dr Jiang Ymin, Dr Steven Peters and Dr Chavie Yenjai for participating in the above experiments and/or the earlier stages of the program. Miss R. Saeeng, Mr T. Liu and Mr K. Kira are thanked for contributing to related chemistry. Dr V. Rukachaisirikul, Dr T. Franz and Mrs Jianmin Li are thanked for their help in the preparation of this manuscript. This research was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan, JSPS-RFTF program, and scholarships from the Hitachi International Foundation, JSPS and Monbusho.

Notes and references

1 *Total Synthesis of Natural Products*: *The 'Chiron' Approach*, Stephen Hanessian, Pergamon, Oxford, 1983.
2 M. Isobe, M. Kitamura and T. Goto, *Chem. Lett*., 1982, 1907; M. Kitamura, M. Isobe, Y. Ichikawa and T. Goto, *J. Org. Chem*., 1984, **49**, 3517; M. Kitamura, M. Isobe, Y. Ichikawa and T. Goto, *J. Am. Chem. Soc*., 1984, **106**, 3252.
3 M. Isobe, *Yukigousei Kagaku Kyoukaishi*, 1994, **52**, 968.
4 (*a*) Y. Ichikawa, K. Tsuboi, Y. Jiang, A. Naganawa and M. Isobe, *Tetrahedron Lett*., 1995, **36**, 7101; (*b*) Y. Jiang and M. Isobe, *Tetrahedron*, 1996, **52**, 2877; (*c*) K. Tsuboi, Y. Ichikawa, Y. Jiang, A. Naganawa and M. Isobe, *Tetrahedron*, 1997, **53**, 5123.
5 M. Isobe, C. Yenjai and S. Tanaka, *Synlett*, 1994, 916; C. Yenjai and M. Isobe, *Tetrahedron*, 1998, **54**, 2509.
6 M. Isobe, Y. Ichikawa and T. Goto, *Tetrahedron Lett*., 1986, **27**, 963; M. Isobe, Y. Ichikawa, D.-L, Bai, H. Masaki and T. Goto, *Tetrahedron*, 1987, **43**, 4767.
7 S. Danishefsky and J. F. Kerwin, *J. Org. Chem*., 1982, **47**, 3803.
8 Y. Ichikawa, M. Isobe, M. Konobe and T. Goto, *Carbohydr. Res*., 1987, **171**, 193.
9 T. Tsukiyama and M. Isobe, *Tetrahedron Lett*., 1992, **33**, 7911.
10 (*a*) Data are partly taken from the Masters Thesis of M. Konobe, Nagoya University (1988); (*b*) T. Nishikawa and M. Isobe, unpublished results.
11 Very recently we have found that trimethylsilyl(propargyl)silane can only react with OTBDPS protection, thus avoiding coordination to $SnCl_4$ due to its steric bulkiness. R. Saeeng and M. Isobe, unpublished results.
12 Data are partly taken from the Master Thesis of T. Tsukiyama, Nagoya University, 1992.
13 T. Tsukiyama, S. C. Peters and M. Isobe, *Synlett*, 1993, 413.
14 A. Herunsalee, M. Isobe, Y. Fukuda and T. Goto, *Synlett*, 1990, 701.
15 M. Isobe, and Y. Jiang, *Tetrahedron Lett*., 1995, **36**, 567.
16 Y. Jiang, Y. Ichikawa and M. Isobe, *Tetrahedron*, 1997, **53**, 5103; K. Tsuboi, Y. Ichikawa and M. Isobe, *Synlett*, 1997, 713.
17 K. C. Nicolaou, C. K. Hwang and M. E. Duggan, *J. Chem. Soc., Chem. Commun*., 1986, 925.
18 D. Zhai, W. Zhai and R. M. Williams, *J. Am. Chem Soc*., 1988, **110**, 2501.
19 C. Leteux and A. Veyrieres, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2647.
20 E. Alvarez, R. Perez, M. Rico, R. M Rodriguez, M. C. Suarez and J. D. Martin, *Synlett*, 1996, 1082.
21 M. Stake, A. Morohashi, H. Oguri, T. Oishi, M. Hirama, N. Harada and T. Yasumoto, *J. Am. Chem. Soc*., 1997, **119**, 11 325.
22 S. Hosokawa, B. Kirschbaum and M. Isobe, *Tetrahedron Lett*., 1998, **39**, 1917.
23 S. Hosokawa and M, Isobe, *Synlett*, 1995, 1179; S. Hosokawa and M. Isobe, *Synlett*, 1996, 351; M. Isobe, S. Hosokawa and K. Kira, *Chem. Lett*., 1996, 473.
24 M. Miljkovic, D. Yeaglley, P. Deslongchamps and Y. L. Dory, *J. Org. Chem*., 1997, **62**, 7597.
25 K. M. Nicholas, *Acc. Chem. Res*., 1987, **20**, 207 and references cited therein.
26 S. Tanaka, T. Tsukiyama and M. Isobe, *Tetrahedron Lett*., 1993, **34**, 5757; S. Tanaka and M. Isobe, *Tetrahedron*, 1994, **50**, 5633.
27 S. Tanaka and M. Isobe, *Tetrahedron Lett*., 1994, **35**, 7801; S. Tanaka, N. Tatsuta, O, Yamashita and M. Isobe, *Tetrahedron*, 1994, **50**, 12 883; S. Tanaka and M. Isobe, *Synthesis*, 1995, 859.
28 H. Greenfield, H. W. Sternberg, R. A. Friedel, J. Wotiz, R. Markby and I. Wender, *J. Am. Chem. Soc*., 1956, **78**, 120.
29 A. V. Muehldorf, A. Guzman-Perez and A. F. Kluge, *Tetrahedron Lett*., 1994, **35**, 8755; S. L. Schreiber, M. T. Klimas and T. Sammakia, *J. Am. Chem. Soc*., 1987, **109**, 5749.
30 M. Saha, B, Baphy and K. M. Nicholas, *Tetrahedron Lett*., 1986, **27**, 915; P. J. Harrington, *Transition Metals in Total Synthesis*, Wiley, New York, 1990, pp. 241–301; T. F. Jamison, S. Shambayati, W. E. Crowe and S. L. Schreiber, *J. Am. Chem. Soc*., 1994, **116**, 5505; C. Mukai, O. Kataoka and M. Hanaoka, *J. Org. Chem*., 1995, **60**, 5910.
31 T. Nakamura, T, Matsui, K. Tanino and I. Kuwajima, *J. Org. Chem*., 1997, **62**, 3032.
32 S. Hosokawa and M. Isobe, *Tetrahedron Lett*., 1998, **39**, 2609.
33 S. Hosokawa and M. Isobe, unpublished results.

Paper 8/04940H