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Formal Total Synthesis of Fostriecin by 1,4-Asymmetric Induction with an Alkyne–Cobalt Complex

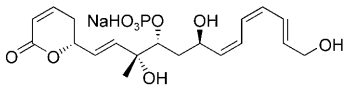
Yujiro Hayashi,*[a] Hirofumi Yamaguchi,[a] Maya Toyoshima,[a] Kotaro Okado,[a] Takumi Toyo,[a] and Mitsuru Shoji[a, b]

Abstract: The synthesis of a protected dephosphofostriecin, and thereby a formal synthesis of fostriecin, has been accomplished. The synthetic challenges were the construction of four stereogenic centers and the conformationally labile *cis-cis-trans*-triene moiety. Previous total syntheses have employed at least two asymmetric reactions that required the use of an external chiral auxiliary. Although remote stereoinduction in a 1,4-relationship is considered difficult, we have developed a notable 1,4-asymmetric induction that utilizes an alkyne–cobalt complex for the control of C5 stereochemistry by the C8 stereogenic center. The stereochemistry at C11 was established by 1,3-asymmetric induction with a higher-order alkynyl-zinc reagent. Thus, only one asymmetric reaction requiring an external chiral auxiliary was employed in this route. The labile *cis-cis-trans*-triene unit was constructed at a late stage of the synthesis by diastereoselective coupling of a dienyne and an aldehyde unit, followed by reduction.

Keywords: alkynes · asymmetric synthesis · cobalt · diastereoselectivity · fostriecin

Introduction

Fostriecin (**1**, CI-920), a novel secondary metabolite isolated from *Streptomyces pulveraceus*, along with analogues such as PD113270 and PD113271,[1] is active in vitro against leukemia, lung cancer, breast cancer, and ovarian cancer and shows antitumor activity against L1210 and P388 leukemia in vivo.[2] It is also known to be a selective inhibitor of protein phosphatase 2A (PP2A) and 4 (PP4).[3] This important biological activity has attracted the attention of many synthetic chemists. In 1997, the relative and absolute configurations of fostriecin were determined by Boger and co-workers by synthetic and degradation studies.[4] The first total synthesis was accomplished by the same group in 2001.[5] Since then several excellent asymmetric syntheses have appeared in the literature,[6,7] as well as a number of synthetic studies.[8]



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Structurally, compound **1** has four stereogenic centers and contains a conformationally labile *cis-cis-trans*-triene moiety. A key issue for the synthesis of **1** is how to control the four stereogenic centers. Most of the previous syntheses are based on reagent-controlled methodology. For instance, all of the previous syntheses employed reagent-based strategies to control the stereogenic center at C5. These strategies included Sharpless asymmetric dihydroxylation,[5] asymmetric hetero-Diels–Alder reaction with a chiral Cr catalyst,[7a] Brown's asymmetric allylation,[7b,f,h,j,l,m] Yamamoto's asymmetric allylation,[7g,i] lithium 2,2′-dihydroxy-1,1′-binaphthyl-ethoxyaluminum hydride (BINAL-H) asymmetric reduction,[7c,d] Sharpless kinetic resolution,[7e] and lipase-catalyzed kinetic resolution.[7k] There are no reported methods for a substrate-controlled strategy.

For the construction of the stereogenic center at C11, two syntheses employed the transfer of chirality from that of natural sources, such as malic acid[7c,d] and glucose.[7j] Only Hatakeyama et al. employed a substrate-controlled method-

[a] Prof. Dr. Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo, Dr. M. Shoji
Department of Industrial Chemistry, Faculty of Engineering
Tokyo University of Science, Kagurazaka, Shinjuku-ku
Tokyo 162-8601 (Japan)
Fax: (+81) 3-5261-4631
E-mail: hayashi@ci.kagu.tus.ac.jp

[b] Dr. M. Shoji
Present address: Faculty of Pharmacy, Keio University
Shibakoen 1-5-30, Minato-ku, Tokyo 105-8512 (Japan)

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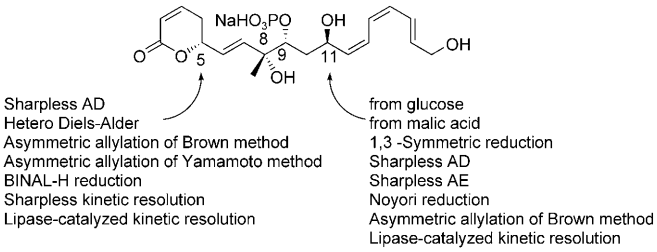
ology; a 1,3-*anti* reduction directed by the stereogenic center at C9.[7f,m] Other total syntheses used reagent-based strategies such as Sharpless asymmetric dihydroxylation,[5] Sharpless asymmetric epoxidation,[7e] Noyori reduction,[7a,h,i,g] Brown's allylation reaction,[7b] and lipase-catalyzed kinetic resolution.[7k]

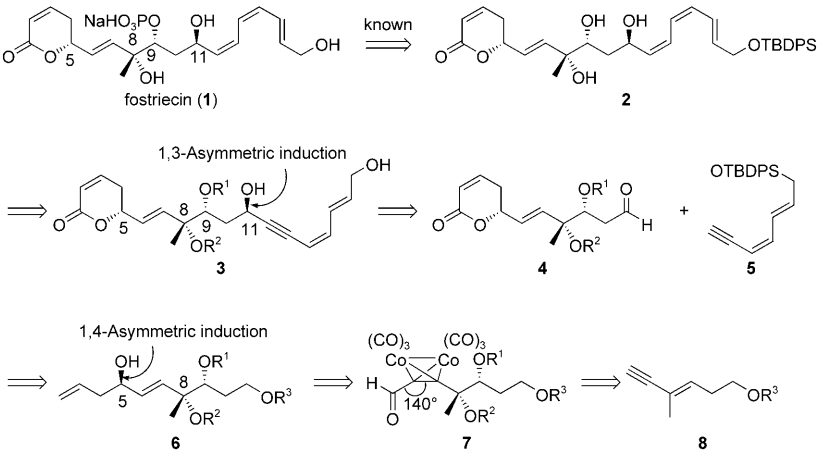
The stereochemistry of all four stereogenic centers was elegantly controlled by four different catalytic asymmetric reactions by the groups of Shibasaki[7g,j] and Falck,[7b] whereas three of the four stereogenic centers were constructed by using asymmetric catalytic reactions in the groups of Jacobsen,[7a] Imanishi,[7c,d] Kobayashi,[7e] and Trost.[7h] In these syntheses, asymmetric catalytic reactions were utilized at least twice (Scheme 1). Yadav et al. employed D-glucose as a chiral starting material and three of the four stereogenic centers were derived from this chiral source.[7j]



Scheme 1. Summary of the control of the absolute configuration at C5 and C11 in previous syntheses of fostriecin (**1**). AD = asymmetric dihydroxylation, AE = asymmetric epoxidation.

Synthetic plan: For the construction of the labile C12–C18 triene moiety, all of the previous methods used a cross-coupling reaction between a C12–C13 vinyl iodide unit and C14–C18 diene metal unit. Though the triene alcohol moiety (C11–C17 unit) would be unstable toward acid, we thought the corresponding dienyne alcohol would be more stable because alkynes are more electron withdrawing than alkenes, and that the triene could be synthesized by stereoselective reduction at a later stage of the synthesis. Based on these considerations, we planned the retrosynthetic analysis outlined in Scheme 2.

Contrary to the previous syntheses, our synthetic strategy is to employ reactions that use pre-existing stereogenic centers to control stereochemistry, if possible. The stereogenic center at C11 was to be constructed, while a new carbon–carbon bond was made between C11 and C12, by 1,3-asymmetric induction directed by the C9 stereogenic center. The

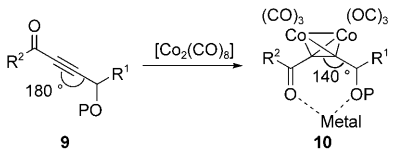


Scheme 2. Retrosynthetic analysis of fostriecin (**1**). TBDPS = *tert*-butyldiphenylsilyl.

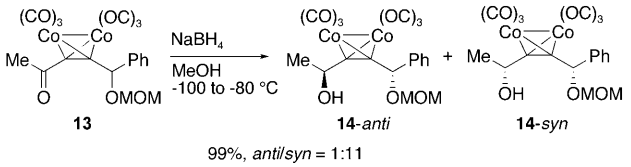
stereochemistry at C5 was to be controlled by the stereogenic center at C8 by 1,4-asymmetric induction triggered by an alkyne–cobalt complex, methodology recently developed in this group (see below).[9] The only reaction requiring the use of an external chiral auxiliary is the Sharpless asymmetric dihydroxylation[10] of the homoallylic alcohol **8**, which would create the two successive stereogenic centers at C8 and C9. To construct the labile triene unit in a synthetically efficient manner, a large triene precursor can be introduced with the creation of the C11 stereogenic center.

Herein, we report the realization of this scenario for the synthesis of protected dephosphofostriecin **2**,[11] the key intermediate from the synthesis reported by Imanishi and coworkers.[7c,d]

Background to the 1,4-asymmetric induction: Chelation control of 1,2- and 1,3-stereorelationships is well established. However, it is a synthetic challenge to control a more remote stereocenter, such as in a 1,4-relationship, by using a pre-existing stereogenic center.[12] In particular, the stereoselective nucleophilic addition of a 4-alkoxy-2-butenal or 2-butynal system is difficult because there are two sp^2 or sp carbon atoms between the stereogenic and pro-stereogenic centers, thus, chelation control is not expected. Metal templates have been utilized for remote asymmetric induction, for example, the elegant 1,5-asymmetric induction described by Ley and co-workers used *p*-allyltricarbonyliron lactone complexes in the total synthesis of taurospongin.[13] There have been, however, no useful methods for efficient 1,4-asymmetric induction that could be applied to the total synthesis of fostriecin. Thus, we have developed a remote asymmetric induction that uses an alkyne–cobalt complex as a metal template.[9] The angle of the triple bond in alkyne **9** is 180°, whereas that in alkyne–cobalt complex **10** is about 140° (Scheme 3).[14] On formation of a complex, the stereogenic and pro-stereogenic centers are be forced closer together and, thus, metal chelation could be expected, which, in turn, would generate a high stereoselectivity. By the use of alkyne–cobalt complexation, we have developed a stereo-

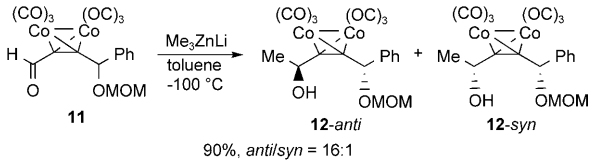


Scheme 3. Change in alkyne bond angle on formation of an alkyne–cobalt complex.



Scheme 5. Stereoselective ketone reduction in an alkyne–cobalt complex.

selective synthetic method for the generation of both the *anti* and *syn* isomers. Excellent *anti* selectivity was obtained in the reaction of alkyne–cobalt complex **11** with Me_3ZnLi (Scheme 4), whereas no selectivity was generated with the uncomplexed alkynyl aldehyde. Reduction of alkyne–cobalt complex **13** with $NaBH_4$ gave *syn*-**14** stereoselectively (Scheme 5) and, again, no selectivity was observed in the reaction of uncomplexed ketone.



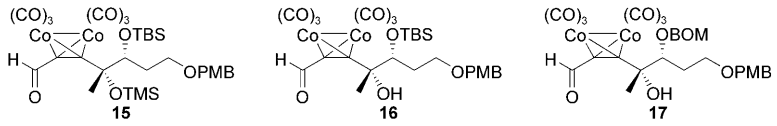
Scheme 4. Stereoselective addition of a alkyl-metal reagent to alkyne–cobalt complex. MOM = methoxymethyl.

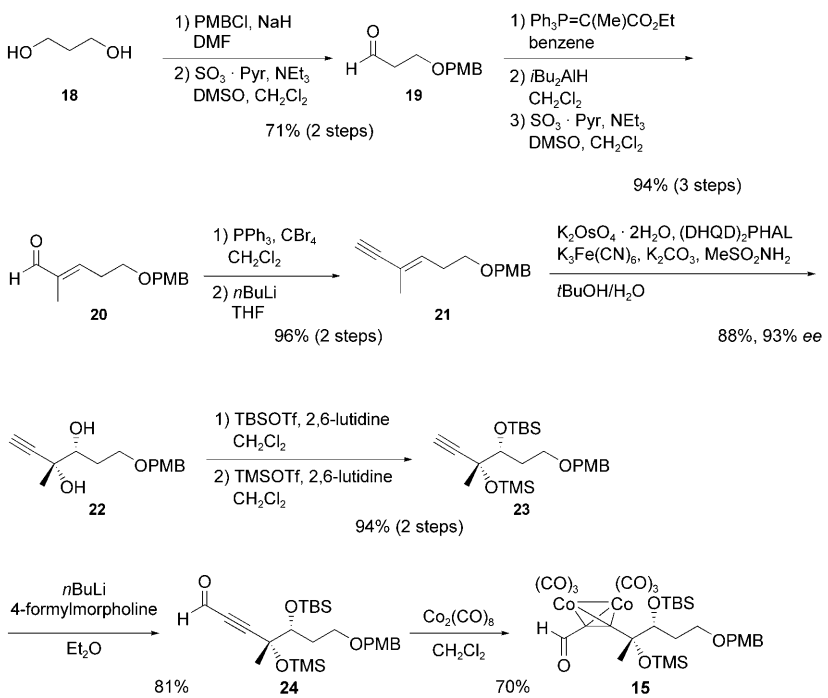
Although it is well known that alkyne–cobalt complexes can be easily prepared under mild oxidative conditions in high yield by treatment of the corresponding alkyne with $[Co_2(CO)_8]$, to the best of our knowledge, there is no literature precedent for the use of alkyne–cobalt complexes for 1,4-asymmetric induction.

Results and Discussion

From our investigations of 1,4-asymmetric induction in alkyne–cobalt complexes, the choice of nucleophile and protecting group for the hydroxyl moiety was found to be important to achieve high selectivity. Based on these results, we selected three alkyne–cobalt complexes with different protecting groups to investigate the 1,4-asymmetric induction for the synthesis of **1**. In complex **15** the hydroxyl groups are protected with nonchelating *tert*-butyldimethylsilyl (TBS) and trimethylsilyl (TMS) groups. In complex **16** one of the hydroxyl groups is TBS-protected and the other is a free hydroxyl group. In **17** one of the hydroxyl groups is protected with a benzyloxymethyl (BOM) group, from which chelation would be possible, and the other hydroxyl group is unprotected. We thought that finding the suitable combination of protecting group and nucleophile to makes this unprecedented 1,4-asymmetric reaction successful was the first key issue in our synthesis of **1**.

Synthesis of alkyne–cobalt complexes 15–17: The synthesis of **15** is described in Scheme 6. Mono-protection of 1,3-propanediol (**18**) with *para*-methoxybenxyl chloride (PMBCl) followed by oxidation with SO_3·pyridine complex[15] provided aldehyde **19**. Wittig reaction, followed by reduction and

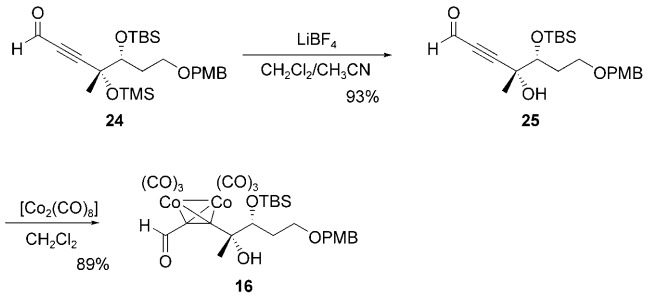




Scheme 6. Synthesis of alkyne–cobalt complex **15**. $(DHQD)_2PHAL$ = Bis(dihydroquinidino)phthalazine.

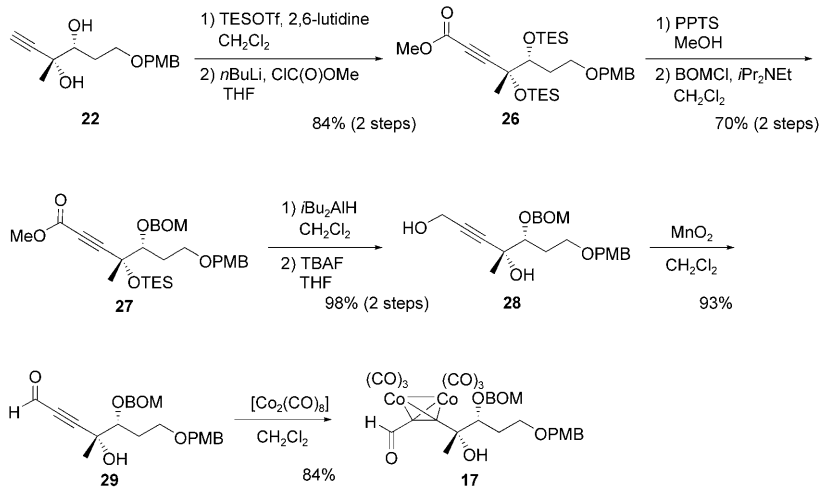
oxidation gave **20**. The Corey–Fuchs alkyne synthesis[16] afforded alkyne **21**, which was oxidized to diol **22** in good yield with excellent enantioselectivity (93% enantiomeric excess (*ee*))[17] under Sharpless dihydroxylation conditions[10]. Protection of the diol **22** with TBS triflate (TBSOTf) and TMSOTf in the presence of 2,6-lutidine gave **23**. Treatment of **23** with BuLi and 4-formylmorpholine gave aldehyde **24**, which was treated with $[Co_2(CO)_8]$ to provide alkyne–cobalt complex **15** in good yield.

The alkyne–cobalt complex **16** was synthesized from **24** in two steps. Selective removal of the TMS group on the *tert*-alcohol in the presence of the secondary TBS ether by treatment with $LiBF_4$, followed by complexation with $[Co_2(CO)_8]$ gave **16** in good yield (Scheme 7).



Scheme 7. Synthesis of alkyne–cobalt complex **16**.

The alkyne–cobalt complex **17** was synthesized from **22** (Scheme 8). Protection of both hydroxyl groups of **22** with triethylsilyl triflate (TESOTf) and 2,6-lutidine, followed by treatment with BuLi and $ClCO_2Me$ gave ester **26**. The protecting group on the secondary alcohol was changed from TES to BOM in two steps to give **27**; treatment with pyridinium *p*-toluenesulfonate (PPTS) in MeOH, then BOMCl and iPr_2NEt. Reduction with diisobutylaluminum hydride (DIBAL-H), followed by treatment with tetra-*n*-butylammonium fluoride (TBAF) gave diol **28**. Oxidation with MnO_2 then gave aldehyde **29**. The treatment of **29** with $[Co_2(CO)_8]$ provided alkyne–cobalt complex **17** in good yield.



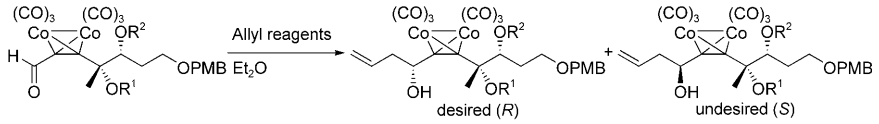
Scheme 8. Synthesis of alkyne–cobalt complex **17**.

Reaction of allyl-metal reagents with alkyne–cobalt complexes 15–17: With complexes **15–17** in hand, the diastereoselective allylation reaction was investigated. First, reaction with Grignard reagent allylmagnesium bromide was examined (Table 1). Only marginal selectivity was observed in the reaction of **17** (Table 1, entry 3) and almost no selectivity was detected in the cases of **15** and **16** (Table 1, entries 1 and 2). Allyl metal reagents $(CH_2{=}CHCH_2)_2Zn$, $(CH_2{=}CHCH_2)_2TiCl_2$, $(CH_2{=}CHCH_2)_2AlEt$, and a combination of $CH_2{=}CHCH_2MgBr$ and $CeCl_3$ also did not afford the desired isomer predominately (Table 1, entries 4–7). In complexes **15–17** the stereogenic center C8 is a quaternary carbon atom and there is an alkoxy group at C9 (fostriecin numbering). Thus, there are several possibilities of chelation and the transition state may be quite different from that of the model reaction in Scheme 4.

As the desired results were not obtained with allyl metal reagents, the Hosomi–Sakurai allylation,[18] which proceeds by a Lewis acid activated mechanism, was investigated. The results are summarized in Table 2. There are reports of the Lewis acid mediated allylation[19] and Mukaiyama-aldol reactions[20] of the dicobalt hexacarbonyl complex of α,β-acetylenic aldehyde, and $BF_3{\cdot}OEt_2$ is a suitable promoter in the reaction with allyl stannanes.[19] The model alkyne–cobalt complex **17** was treated with allyl triphenyl stannane in the presence of several Lewis acids. Whereas low selectivity was observed with $HfCl_4$, $ZnCl_2$, $BF_3{\cdot}OEt_2$, $TiCl_3(OiPr)$, and $TiCl(OiPr)_3$ (Table 2, entries 1–3, 5, and 6), moderate selectivity (73:27) was obtained when $MgBr_2{\cdot}OEt_2$ was employed (Table 2, entry 4). Good selectivity (80:20) was obtained in the presence of $TiCl_2(OiPr)_2$ (Table 2, entry 7). The selectivity increased to 92:8 when the reaction was performed at lower temperature (−40 °C, Table 2, entry 8). It should be mentioned that the bulkiness of the allyl stannane reagent is important. Whereas $Ph_3SnCH_2CH{=}CH_2$ gave an excellent result, the corresponding Bu_3Sn analogue gave poor selectivity (Table 2, entry 8 versus 9). The absolute configuration of the newly generated stereocenter at C5 of **32** was determined by the advanced Mosher's α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) method[21] after conversion to the (*R*)- and (*S*)-mono-MTPA esters of **32**.

1,3-Asymmetric induction: As the crucial 1,4-asymmetric induction had been successful, the next key issue was the coupling of the C1–C11 and C12–C18 units, which generates the stereogenic center at C11

Table 1. The effect of allyl metal reagent on the 1,4-asymmetric induction in alkyne–cobalt complexes **15**–**17**.[a]



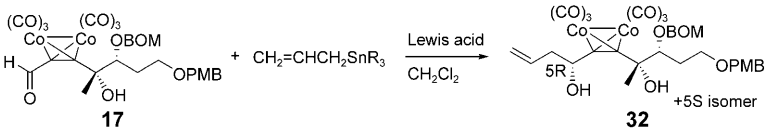
15 : R^1 = TMS, R^2 = TBS
16 : R^1 = H, R^2 = TBS
17 : R^1 = H, R^2 = BOM

30 : R^1 = TMS, R^2 = TBS
31 : R^1 = H, R^2 = TBS
32 : R^1 = H, R^2 = BOM

Entry	Complex	Reagent	T [°C]	t [min]	Yield [%][b]	Ratio R/S[c]
1	**15**	allylMgBr	−90	30	38	50:50
2	**16**	allylMgBr	−90	20	50	50:50
3	**17**	allylMgBr	−78	30	87	55:45
4	**17**	$(allyl)_2Zn$	−78	10	87	60:40
5	**17**	allylMgBr+$CeCl_3$	−78	360	80	50:50
6	**17**	$(allyl)_2TiCl_2$	−78	10	82	51:49
7	**17**	$(allyl)_2AlEt$	−78–0	600	80	51:49

[a] Alkyne–cobalt complex (0.04 mmol), allyl metal reagent (0.09 mmol), Et_2O (0.30 mL), 20 min. [b] Isolated yield. [c] *R*/*S* ratio at C5 (fostriecin numbering), determined by ^1H NMR spectroscopic analysis.

Table 2. The effect of the Lewis acid on 1,4-asymmetric induction in the reaction between **17** and allyl stannanes.[a]



17 **32**

Entry	R	Lewis acid	T [°C]	t	Yield [%][b]	Ratio R/S[c]
1	Ph	$HfCl_4$	−78	0.5 h	15	50:50
2	Ph	$ZnCl_2$	−78	4 h	45	55:45
3	Ph	BF_3OEt_2·OEt_2	−78	10 min	40	64:36
4	Ph	$MgBr_2$·OEt_2	−78 to 0	8 h	86	73:27
5	Ph	$TiCl_3(OiPr)$	−78	0.5 h	20	60:40
6	Ph	$TiCl(OiPr)_3$	−78 to 0	8 h	78	60:40
7	Ph	$TiCl_2(OiPr)_2$	−20	4 h	60	80:20
8	Ph	$TiCl_2(OiPr)_2$	−40	46 h	60	92:8
9	Bu	$TiCl_2(OiPr)_2$	−45	12 h	86	45:55

[a] Alkyne–cobalt complex **17** (0.04 mmol), allyl stannane (0.40 mmol), Lewis acid (0.40 mmol), CH_2Cl_2 (2 mL). [b] Isolated yield. [c] *R*/*S* ratio at C5 (fostriecin numbering), determined by HPLC analysis.

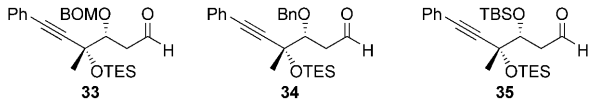
through 1,3-asymmetric induction directed by the C9 stereogenic center (see Scheme 2).

There are several reports on chelation-controlled 1,3-asymmetric induction in the literature. Reetz and Jung reported that 1,3-asymmetric induction in the reaction of 3-benzyloxybutanal and $MeTiCl_3$ afforded the *anti* isomer of the product with 80% diastereomeric excess (*de*).[22] Marshall and Jahns observed *anti*-selective addition of an alkynyl lithium reagent to β-*tert*-butyldimethylsiloxyaldehyde in the presence of LiBr,[23] and the *anti* isomer was predominately obtained in the Lewis acid mediated addition of alkynyl stannanes to β-siloxyaldehydes reported by Evans and co-workers.[24]

The stereoselective coupling of the C1–C11 and C12–C18 units was expected to be facile because of this precedent, however, this was not the case and a model study had to be carried out. The results obtained by Evans et al.[24] suggested that the combination of the hydroxyl-protecting group, nucleophile, and additive would be important for the success of this 1,3-asymmetric induction. Three aldehydes (**33**–**35**) with different protecting groups were selected as model aldehydes for the C1–C11 unit.

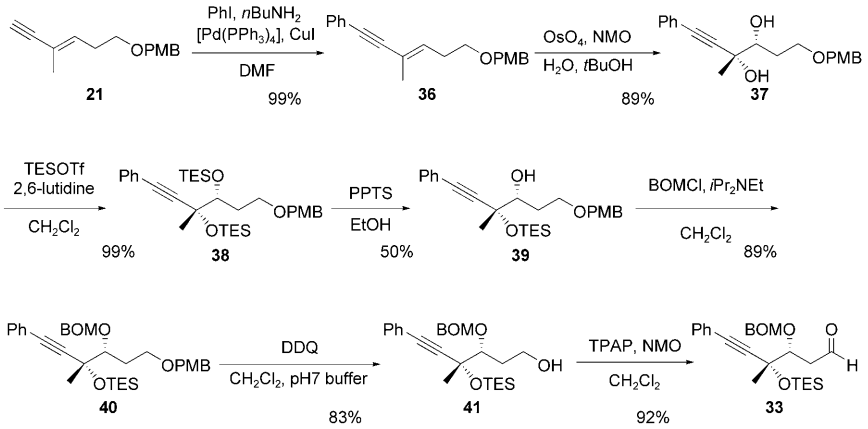
Synthesis of aldehydes 33–35: Aldehyde **33** was synthesized from the C1–C11 unit intermediate **21** as shown in Scheme 9. Sonogashira coupling[25] of alkyne **21** with phenyl iodide proceeded smoothly to afford enyne **36**. Dihydroxylation promoted by a catalytic amount of OsO_4 afforded diol **37** in good yield. The TES-protection of both hydroxyl groups, followed by selective removal from the secondary alcohol gave **39**. Treatment of **39** with BOMCl then removal of the PMB group with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[26] afforded primary alcohol **41**. Oxidation of alcohol **41** with tetrapropylammonium perruthenate (TPAP)[27] gave aldehyde **33** in good yield.

Aldehyde **34** was prepared from diol **37** (Scheme 10). Removal of the PMB protecting group with trifluoroacetic acid (TFA), followed by treatment with benzaldehyde dimethyl acetal in the presence of toluene sulfonic acid (TsOH) afforded **43**. Protection of the *tert*-alcohol with TESOTf and 2,6-lutidine gave **44**. Reduction of **44** with DIBAL-H afforded primary alcohol **45**, which was oxidized with TPAP to afford **34**.

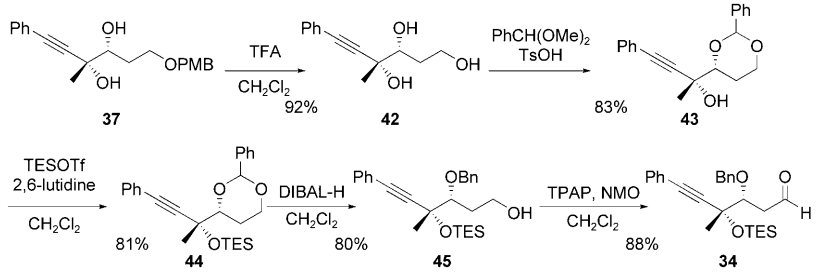


33 **34** **35**

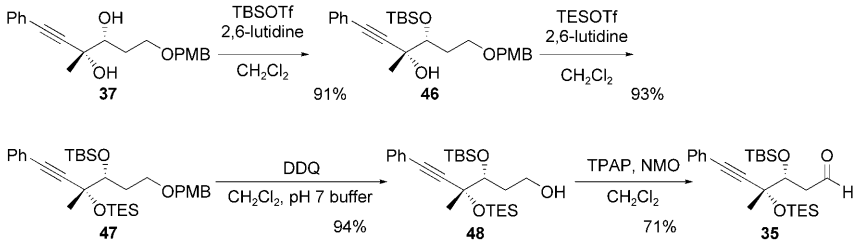
Aldehyde **35** was also synthesized from diol **37** (Scheme 11). Successive protection of the secondary and tertiary hydroxyl groups of **37** with TBSOTf and TESOTf, respectively, afforded **47**. Removal of the PMB group and oxidation of the primary hydroxyl group with TPAP provided **35**.



Scheme 9. Synthesis of model aldehyde **33** (NMO = *N*-methylmorpholine-*N*-oxide).



Scheme 10. Synthesis of model aldehyde **34**.



Scheme 11. Synthesis of model aldehyde **35**.

1,3-Asymmetric induction: Reaction of 33–35 with phenylacetylene: Phenylacetylene was selected as a model for the C12–C18 dienyne unit and the coupling reaction with aldehydes **33**–**35** was investigated. Chelation would be expected in the reactions of **33** and **34**, whereas it would not be expected in the case of bis-silyl-protected ether **35**. The results are summarized in Table 3. Use of LiBr in addition to the alkynyl lithium reagent gave low diastereoselectivity (Table 3, entries 1 and 2) and alkynyl titanium reagents, prepared by addition of $TiCl(OiPr)_3$ or $TiCl_2(OiPr)_2$, afforded the undesired *syn* isomer predominately (Table 3, entries 3–8). Alkynyl zinc (Table 3, entries 9 and 10) and aluminum reagents (Table 3, entries 11 and 12) also did not afford good results.

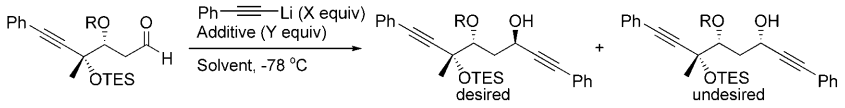
Next, the Lewis acid was investigated. Me_2AlCl, $MeAlCl_2$ or $BF_3{\cdot}OEt_2$ were selected because $BF_3{\cdot}OEt_2$ is reported to afford the desired selectivity.[24] As shown in Table 4, the reaction proceeds in some cases, but the desired *anti* isomer was only obtained with low selectivity (Table 4, entry 4) or as the minor isomer.

These inferior results can be explained by the presence of bulky substituents at C8 (fostriecin numbering). That is, because the chair transition state **53** cannot be formed as a result of the steric bulk at C8, the expected 1,3-asymmetric induction cannot be realized (Scheme 12).

To realize the 1,3-asymmetric induction, we thought as follows: If the hydroxyl groups at C8 and C9 were protected as a cyclic acetal the conformation would be fixed. If the reaction proceeds through transition state **55** (shown in Scheme 13), in which chelation would be possible, the desired *anti* isomer should be generated predominantly. With this transition state in mind, model aldehyde **54** was synthesized from the previous precursor **37** by formation of acetal **57** with acetone dimethyl acetal, followed by the removal of PMB and oxidation of alcohol **58** with TEMPO[28] (Scheme 14).

The crucial 1,3-asymmetric induction was investigated in detail with model aldehyde **54**. After several trials, the choice of the metal was found to be important. Whereas lithium and titanium acetylide gave no selectivity (Table 5, entries 1 and 2), reaction with the zinc derivative gave good results (Table 5, entry 3). The ratio of alkynyl lithium to $ZnBr_2$ is crucial to achieve the best selectivity (Table 5, entries 3–5) and dialkynyl zinc was found the most suitable nucleophile (Table 5, entry 4), which was also used by Fukuyama and co-workers in the total synthesis of leustroducsin B.[29] Excellent *anti* selectivity and good yield were obtained with a 2:1 ratio of alkynyl lithium/zinc additive (Table 5, entry 4).

Table 3. The effect of the alkynyl-metal reagent on the 1,3-asymmetric induction.[a]



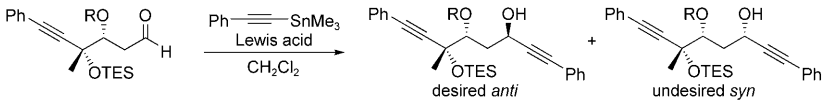
33 : R = BOM
34 : R = Bn
35 : R = TBS

49 : R = BOM
50 : R = Bn
51 : R = TBS

Entry	Aldehyde	Additive	X/Y[b]	Solvent	Yield [%][c]	Ratio *anti*/*syn*[d]
1	**33**	LiBr	1:3	THF	50	50:50
2	**35**	LiBr	1:3	THF	63	58:42
3	**33**	$TiCl(OiPr)_3$	1:1	toluene/THF	99	14:86
4	**34**	$TiCl(OiPr)_3$	1:1	toluene/THF	99	47:53
5	**35**	$TiCl(OiPr)_3$	1:1	toluene/THF	90	17:83
6	**33**	$TiCl_2(OiPr)_2$	1:1	toluene/THF	80	22:78
7	**34**	$TiCl_2(OiPr)_2$	1:1	toluene/THF	90	52:48
8	**35**	$TiCl_2(OiPr)_2$	1:1	toluene/THF	90	25:75
9	**33**	$ZnBr_2$	2:1	Et_2O	99	33:67
10	**33**	$ZnBr_2$	1:1	Et_2O	45	38:62
11	**33**	Me_2AlCl	1:1	THF	85	50:50
12	**35**	Me_2AlCl	1:1	THF	90	60:40

[a] Phenylacetylene (0.30 mmol), BuLi (0.20 mmol), Lewis acid (0.11 mmol), aldehyde (5.50 μmol), solvent (0.30 mL), −78 °C, 2 h. [b] Ratio of alkynyl lithium/additive. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopy of the crude product.

Table 4. The effect of Lewis acid in the 1,3-asymmetric induction.[a]

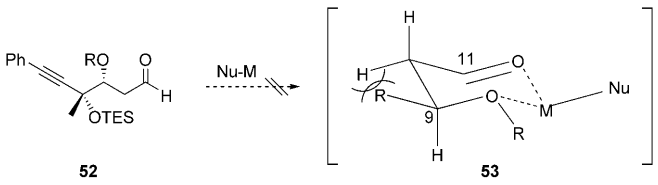


33 : R = BOM
34 : R = Bn
35 : R = TBS

49 : R = BOM
50 : R = Bn
51 : R = TBS

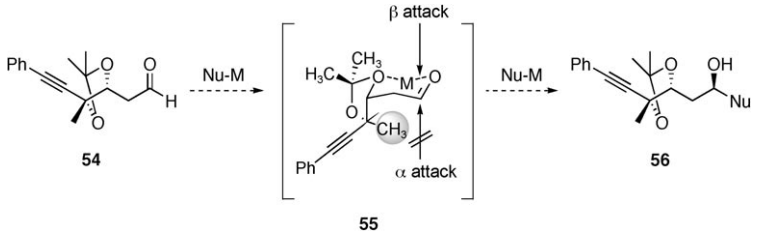
Entry	Aldehyde	Lewis acid	*T* [°C]	Yield [%][b]	Ratio *anti*/*syn*[c]
1	**33**	Me_2AlCl	−90	70	21:79
2	**35**	Me_2AlCl	−90	decomp.[d]	nd[e]
3	**33**	$MeAlCl_2$	−78	70	23:77
4	**34**	$MeAlCl_2$	−78	60	69:31
5	**35**	$MeAlCl_2$	−78	decomp.	nd
6	**33**	$BF_3{\cdot}OEt_2$	−78	90	52:48

[a] Phenylacetylene (0.30 mmol), BuLi (0.20 mmol), Lewis acid (0.11 mmol), aldehyde (5.50 μmol), Et_2O (0.30 mL), 2 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy of the crude product. [d] Decomposition of the starting material. [f] Not determined.



52 **53**

Scheme 12. Postulated transition state for the reaction of **52**.



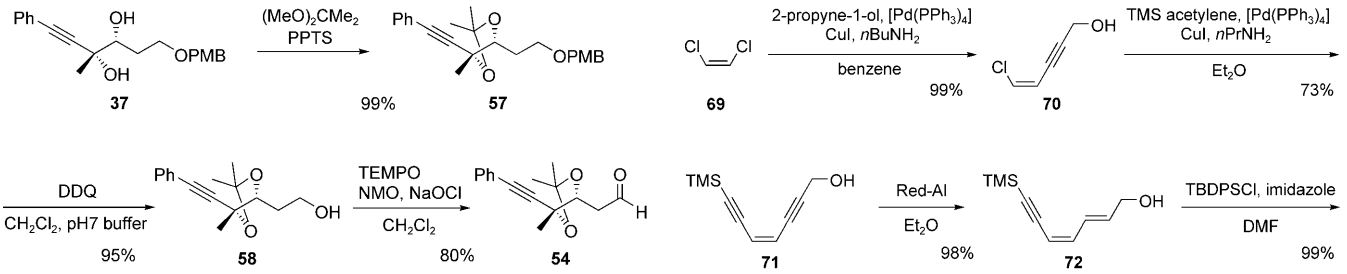
54 **55** **56**

Scheme 13. Postulated transition state for the reaction of **54**.

Synthesis of the aldehyde (C1–C11) unit: With conditions for the coupling reaction established for the model compound **54**, the synthesis of the C1–C11 coupling unit **68** from alkyne–cobalt complex **32** was investigated (Scheme 15). Cobalt was quantitatively removed from **32** by treatment with NMO and subsequent reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) gave *trans* alkene **62** selectively, in good yield. The unsaturated lactone moiety **63**, which was constructed by acylation with acryloyl chloride, was exposed to the Grubbs second-generation catalyst[30] to afford **64** in quantitative yield. Cleavage of the BOM group afforded the diol **65**, which is an intermediate from the synthesis of Hatakeyama et al.[7f,l,m] Compound **65** was protected as its dimethyl acetal **66** and subsequent removal of the PMB protecting group, followed by TEMPO oxidation[28] afforded key intermediate **68**.

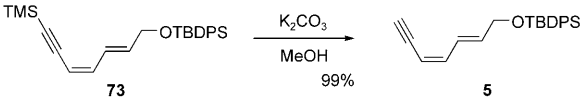
Synthesis of the dienyne (C12–C18) unit: The coupling partner, dienyne **5**, was synthesized stereoselectively from *cis*-1,2-dichloroethene (**69**) by two successive Sonogashira reactions with 2-propyne-1-ol and trimethylsilylacetylene to generate enyne derivative **71** in good yield (Scheme 16). Stereoselective reduction with Red-Al,[31] followed by protection of the hydroxyl group with TBDPSCl and deprotection of the TMS group with K_2CO_3 afforded **5** in good yield.

Coupling of the C1–C11 and C12–C18 units and completion of the formal total synthesis of 1: The crucial coupling reaction of aldehyde **68** and dienyne **5** was performed by using the conditions developed with the model substrates (Scheme 17). The alkynylzinc reagent generated from **5** reacted smoothly with **68** to give **74** in good yield, with excellent diastereoselectiv-



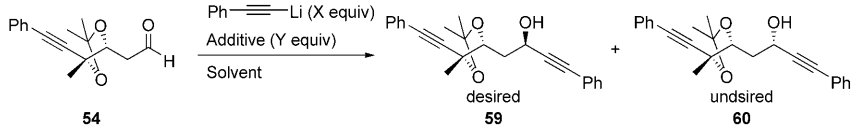
Scheme 14. Synthesis of model aldehyde **54**.

ity. Treatment of **74** with TFA removed both the acetal and TBDPS groups to yield tetraol **75**. Protection of the primary alcohol with TBDPSCl gave **76**. The labile triene unit **2** was successfully constructed in good yield by reduction with Rieke Zn[32] in the presence of buffer solution. The conversion of **2** to **1** has been demonstrated by Imanishi and coworkers,[7c,d] thus, the formal total synthesis of **1** has been accomplished.



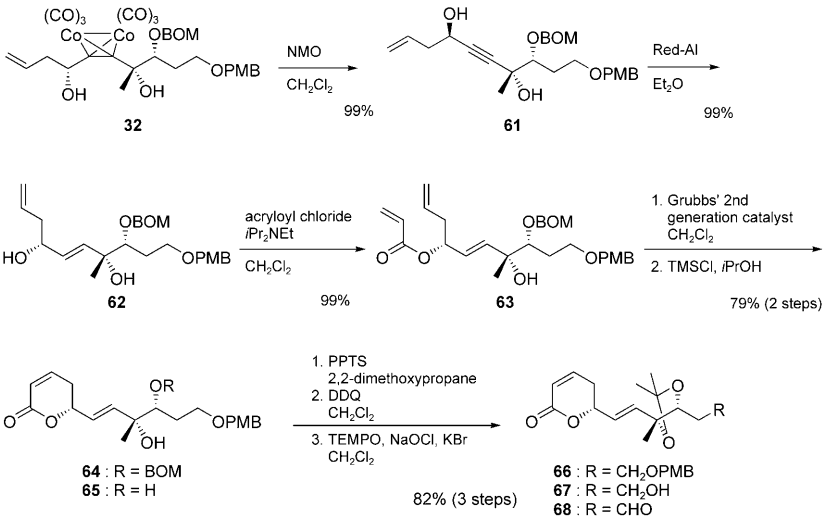
Scheme 16. Synthesis of the C12–C18 dienyne unit **5**.

Table 5. The effect of the nucleophile in the reaction of **54** with alkynyl metal.[a]



Entry	Additive	X/Y	Solvent	*T* [°C]	Yield [%][b]	Ratio *anti*/*syn*[c]
1	none	–	THF	−78	60	45:55
2	$TiCl(OiPr)_3$	1:1	toluene/THF	−78	90	50:50
3	$ZnBr_2$	1:1	Et_2O	−78 to −20	70	72:28
4	$ZnBr_2$	2:1	Et_2O	−78 to −20	90	91:9
5	$ZnBr_2$	3:1	Et_2O	−78 to −50	50	90:10

[a] Phenylacetylene (0.29 mmol), BuLi (0.20 mmol), Lewis acid (0.11 mmol), aldehyde (19.2 μmol), solvent (0.30 mL). [b] Isolated yield. [c] Determined by HPLC.



Scheme 15. Synthesis of the C1–C11 aldehyde unit **68** from alkyne–cobalt complex **32**.

Conclusion

We have accomplished the synthesis of protected dephosphofostriecin **2**, and thereby a formal synthesis of fostriecin (**1**). Two of the four stereogenic centers were generated with an external chiral reagent by Sharpless asymmetric dihydroxylation. The other two were synthesized stereoselectively: one by a novel 1,4-asymmetric induction within an alkyne–cobalt complex developed by our group,[9] the second by 1,3-asymmetric induction. Although cobalt has been used in many types of reaction,[33–40] the present reaction is the first successful example of the use of a cobalt complex in 1,4-asymmetric induction.

Acknowledgements

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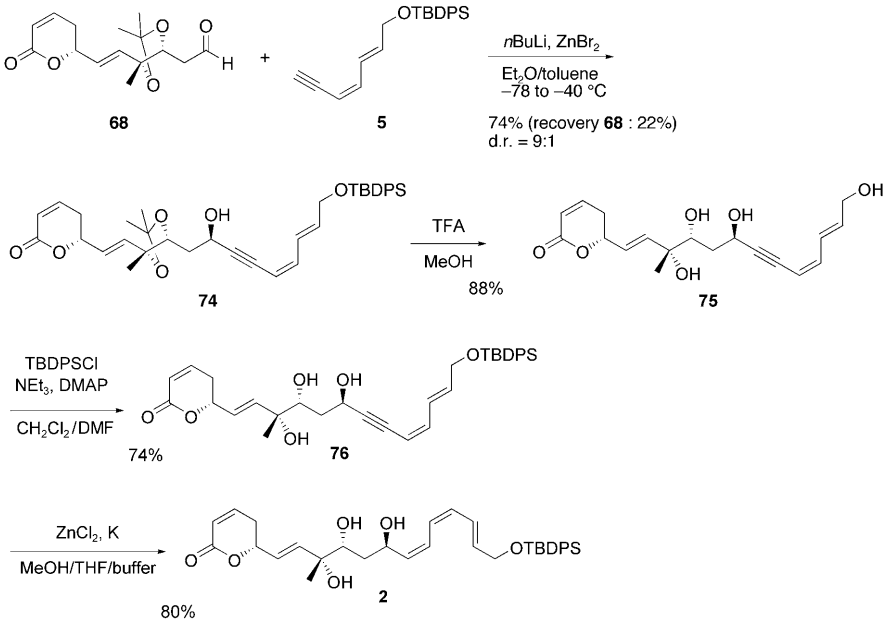

Scheme 17. Synthesis of Imanishi's intermediate **2** from **68** and **5**.

[1] a) J. B. Tunac, B. D. Graham, W. E. Dobson, *J. Antibiot.* **1983**, *36*, 1595; b) S. S. Stampwala, R. H. Bunge, T. R. Hurley, N. E. Willmer, A. J. Brankiewicz, C. E. Steinman, T. A. Smitka, J. C. French, *J. Antibiot.* **1983**, *36*, 1601.

[2] a) S. S. Stampwala, R. H. Bunge, T. R. Hurley, N. E. Willmer, A. J. Brankiewicz, C. E. Steinman, T. A. Smitka, J. C. French, *J. Antibiot.* **1983**, *36*, 1601; b) R. S. De Jong, E. G. E. De Vries, N. H. Mulder, *Anti-Cancer Drugs* **1997**, *8*, 413; c) W. Scheithauer, D. D. V. Hoff, G. M. Clark, J. L. Shillis, E. F. Elslager, *Eur. J. Clin. Oncol.* **1986**, *22*, 921.

[3] For reviews, see: a) D. S. Lewy, C. M. Gauss, D. R. Soenen, D. L. Boger, *Curr. Med. Chem.* **2002**, *9*, 2005; b) A. McCluskey, A. T. R. Sim, J. A. Sakoff, *J. Med. Chem.* **2002**, *45*, 1151.

[4] D. L. Boger, M. Hikota, B. M. Lewis, *J. Org. Chem.* **1997**, *62*, 1748.

[5] D. L. Boger, S. Ichikawa, W. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 4161.

[6] For reviews, see: a) M. Shibasaki, M. Kanai, *Heterocycles* **2005**, *66*, 727; b) K. Miyashita, M. Ikejiri, T. Tsunemi, A. Matsumoto, T. Imanishi, *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 874.

[7] a) D. E. Chavez, E. N. Jacobsen, *Angew. Chem.* **2001**, *113*, 3779; *Angew. Chem. Int. Ed.* **2001**, *40*, 3667; b) Y. K. Reddy, J. R. Falck, *Org. Lett.* **2002**, *4*, 969; c) K. Miyashita, M. Ikejiri, H. Kawasaki, S. Maemura, T. Imanishi, *Chem. Commun.* **2002**, 742; d) K. Miyashita, M. Ikejiri, H. Kawasaki, S. Maemura, T. Imanishi, *J. Am. Chem. Soc.* **2003**, *125*, 8238; e) Y. G. Wang, Y. Kobayashi, *Org. Lett.* **2002**, *4*, 4615; f) T. Esumi, N. Okamoto, S. Hatakeyama, *Chem. Commun.* **2002**, 3042; g) K. Fujii, K. Maki, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 733; h) B. M. Trost, M. U. Frederiksen, J. P. N. Papillon, P. E. Harrington, *J. Am. Chem. Soc.* **2005**, *127*, 3666; i) K. Maki, R. Motoki, K. Fujii, M. Kanai, T. Kobayashi, S. Tamura, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 17111; j) J. S. Yadav, I, Prathap, B. P. Tadi, *Tetrahedron Lett.* **2006**, *47*, 3773; k) O. Robles, F. E. McDonald, *Org. Lett.* **2009**, *11*, 5498; l) S. M. Sarkar, E. N. Wanzala, S. Shibahara, K. Takahashi, J. Ishihara, S. Hatakeyama, *Chem. Commun.* **2009**, 5907; m) S. Shibahara, M. Fujino, Y. Tashiro, N. Okamoto, T. Esumi, K. Takahashi, J. Ishihara, S. Hatakeyama, *Synthesis* **2009**, 2935.

[8] a) G. Just, B. Oconnor, *Tetrahedron Lett.* **1988**, *29*, 753; b) S. Y. Liu, D. F. Huang, H. H. Huang, L. Huang, *Chin. Chem. Lett.* **2000**, *11*, 957; c) J. Cossy, F. Pradaux, S. BouzBouz, *Org. Lett.* **2001**, *3*, 2233; d) Y. Kiyotsuka, J. Igarashi, Y. Kobayashi, *Tetrahedron Lett.* **2002**, *43*, 2725; e) J. A. Marshall, M. P. Bourbeau, *Org. Lett.* **2003**, *5*, 3197; f) P. V. Ramachandran, H. P. Liu, M. V. R. Reddy, H. C. Brown, *Org. Lett.* **2003**, *5*, 3755.

[9] Y. Hayashi, H. Yamaguchi, M. Toyoshima, S. Nasu, K. Ochiai, M. Shoji, *Organometallics* **2008**, *27*, 163.

[10] H. C. Kolbe, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[11] A preliminary communication of this work has been reported, see: Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo, M. Shoji, *Org. Lett.* **2008**, *10*, 1405.

[12] For a review, see; a) H. J. Mitchell, A. Nelson, S. Warren, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1899; b) H. Sailes, A. Whiting, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1785; c) K. Mikami, M. Shimizu, H.-C. Zhang, B. E. Maryanoff, *Tetrahedron* **2001**, *57*, 2917.

[13] C. J. Hollowood, S. V. Ley, S. Yamanoi, *Chem. Commun.* **2002**, 1624.

[14] a) W. G. Sly, *J. Am. Chem. Soc.* **1959**, *81*, 18; b) B. J. Rausch, R. Gleiter, F. Rominger, *J. Chem. Soc. Dalton Trans.* **2002**, 2219.

[15] J. R. Parikh, W. V. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505.

[16] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769.

[17] The enantioselectivity of **22** was determined by chiral HPLC analysis (Chiralcel OD-H column, $\lambda = 254$ nm, *i*PrOH/hexane 1:20, 1.0 mL min^{-1}; $t_R = 24.1$ min (major), 20.7 min (minor)).

[18] a) A. Hosomi, M. Endo, H. Sakurai, *Chem. Lett.* **1976**, 941; b) A. Hosomi, H. Sakurai, *Tetrahedron Lett.* **1976**, *17*, 1295.

[19] S. Balduzzi, M. A. Brook, M. J. McGlinchey, *Organometallics* **2005**, *24*, 2617.

[20] For a review, see; C. Mukai, M. Hanaoka, *Synlett* **1996**, 11.

[21] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.

[22] T. M. Reetz, A. Jung, *J. Am. Chem. Soc.* **1983**, *105*, 4833.

[23] J. Marshall, B. A. Jahns, *J. Org. Chem.* **1998**, *63*, 7885.

[24] D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322.

[25] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.

[26] K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron* **1986**, *42*, 3021.

[27] W. P. Griffith, S. V. Ley, *Aldrichimica Acta* **1990**, *23*, 13.

[28] P. L. Anelli, F. Montanari, S. Quici, *Org. Synth. Coll.* **1993**, *8*, 367.

[29] K. Shimada, Y. Kaburagi, T. Fukuyama, *J. Am. Chem. Soc.* **2003**, *125*, 4048.

[30] a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953; b) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18.

[31] a) K.-K. Chan, A. C. Specian, Jr., G. Saucy, *J. Org. Chem.* **1978**, *43*, 3435; b) T. K. Jones, S. E. Denmark, *Org. Synth. Coll.* **1990**, *7*, 524.

[32] a) R. D. Rieke, S. J. Uhm, *Synthesis* **1975**, 452; b) W. N. Chou, D. L. Clark, J. B. White, *Tetrahedron Lett.* **1991**, *32*, 299.

[33] R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1980**, *102*, 5253.

[34] Reviews, see; a) P. L. Pauson, *Tetrahedron* **1985**, *41*, 5855; b) S. E. Gibson (née Thomas), A. Stevenazzi, *Angew. Chem.* **2003**, *115*, 1844; *Angew. Chem. Int. Ed.* **2003**, *42*, 1800; c) J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32.

[35] T. F. Jamison, S. Sharmbayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1994**, *116*, 5505.
[36] For reviews, see: a) K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207; b) T. J. J. Müller, *Eur. J. Org. Chem.* **2001**, 2021; c) B. J. Teobald, *Tetrahedron* **2002**, *58*, 4133.
[37] For a recent nice example, see: A. Hamajima, M. Isobe, *Angew. Chem.* **2009**, *121*, 2985; *Angew. Chem. Int. Ed.* **2009**, *48*, 2941.
[38] N. Iwasawa, K. Inaba, S. Nakayama, M. Aoki, *Angew. Chem.* **2005**, *117*, 7613; *Angew. Chem. Int. Ed.* **2005**, *44*, 7447.
[39] K. Tanino, K. Onuki, K. Asano, M. Miyashita, T. Nakamura, Y. Takahashi, I. Kuwajima, *J. Am. Chem. Soc.* **2003**, *125*, 1498.
[40] a) W. R. Roush, J. C. Park, *Tetrahedron Lett.* **1991**, *32*, 6285; b) P. Ganesh, K. M. Nicholas, *J. Org. Chem.* **1997**, *62*, 1737.

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