The β-elimination route to stereodefined γ-alkylidenebutenolides†

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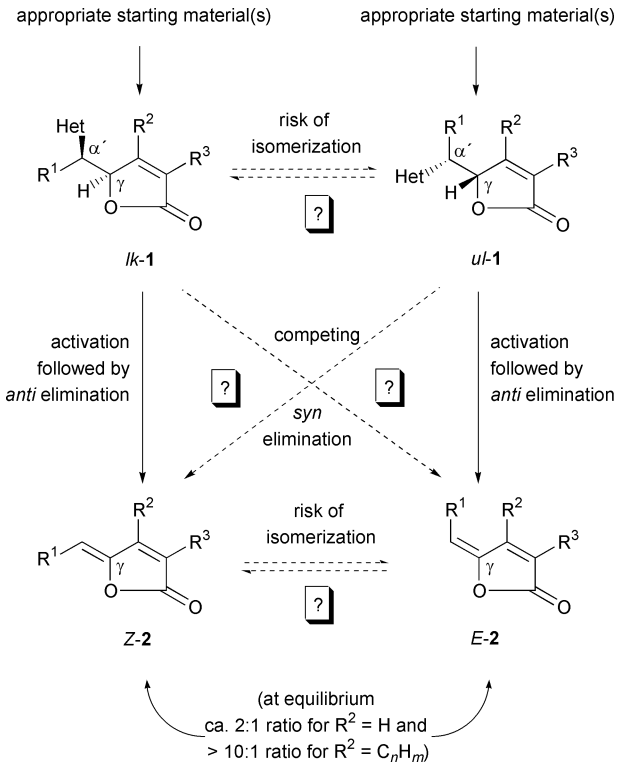
γ-Alkylidenebutenolides are biologically significant compounds and comprise compounds as structurally and functionally diverse as the inhibitor dihydroxerulin (*Z*-61, Scheme 16) of cholesterol biosynthesis or the carotinoid peridinin (*Z*-18a, Scheme 5) which plays a dominant role in marine photosynthesis. For the stereo-controlled obtention of γ-alkylidenebutenolides *Z*-2 or *E*-2 with or without alkyl substituents at C-α or C-β, a general strategy has been developed (Scheme 1). The key step of this strategy is the stereospecific *anti*-elimination of water from diastereopure γ-(α-hydroxyalkyl)butenolides *lk*-1 or *ul*-1—be they racemic or enantiopure (*lk* = like, *ul* = unlike: γ-(α-hydroxyalkyl)butenolides *lk*-1 give γ-alkylidenebutenolides *Z*-2, while γ-(α-hydroxyalkyl)butenolides *ul*-1 furnish the isomeric γ-alkylidenebutenolides *E*-2. As dehydrating agents we used mixtures of triflic anhydride and pyridine or of diethyl azodicarboxylate and triphenylphosphine. Previous β-eliminations providing γ-alkylidenebutenolides exhibited in general little stereoselectivity and no stereospecifity at all (exception: Scheme 10), irrespective of whether this β-elimination was performed separately or took place *in situ*.

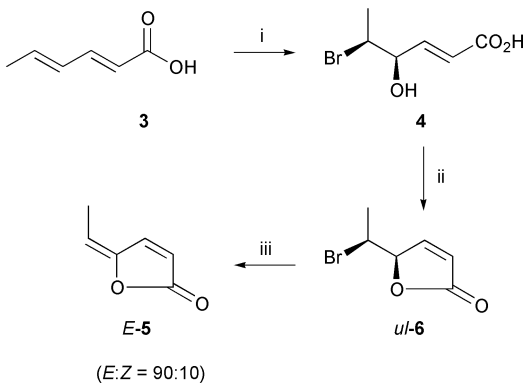
Introduction

Butenolides are γ-butyrolactones with a $C^{\alpha}=C^{\beta}$ bond. They abound in nature, revealing a great variety of substitution patterns.[1] Among many others, one finds γ-alkylidenebutenolides. The most prominent representatives of this class are vitamin C, the pulvinic acids [α-aryl-β-hydroxy-γ-(α-carboxybenzylidene)butenolides], the pulvinones [α-aryl-β-hydroxy-γ-(benzylidene)butenolides], and derivatives thereof. However, there are also γ-alkylidenebutenolides which are totally devoid of heteroatom substituents at C^{α} or C^{β}. Several such γ-alkylidenebutenolides are biologically significant.

Their simplest conceivable representative is γ-methylenebutenolide. This is a natural product ('protoanemonin'[2]) and known to be an antibiotic. The highly unsaturated γ-alkylidenebutenolides dihydroxerulin (*Z*-**61**, Scheme 16) and xerulin (*trans*,*Z*-**66**, Scheme 17) are structurally unique, intensely yellow fungal colorants.[3] Isolated as 90 : 10–65 : 35 mixtures, they were found to inhibit the biosynthesis of cholesterol without being cytotoxic; they prevent the incorporation of ^{14}C-acetate—but not of ^{14}C-mevalonic acid—into cholesterol produced from HeLa S3 cells (ID_{50} = 1 μg g^{-1}).[3] Suppressing a different step of the biosynthesis of cholesterol is what three



Scheme 1 Strategy for the stereoselective generation of γ-alkylidenebutenolides by *anti*-eliminations from γ-(α-hydroxyalkyl)butenolides.



Scheme 2 *Reagents*: i, Br_2, H_2O, 35% **4** + 33% re-isolated **3**; ii, HCl, H_2O, h*ν*, 70%; iii, NEt_3, CH_2Cl_2, 91%.

† Dedicated to Dr Klaus Brückner (retired from Cela-Merck, Ingelheim) on the occasion of his 75th birthday.

Reinhard Brückner prepared his doctoral thesis at the Ludwig-Maximilians-Universität München under the supervision of Professor Rolf Huisgen (1984) and was a postdoctoral fellow with Professor Paul A. Wender at Stanford University. After a habilitation with Professor Reinhard W. Hoffmann at the Philipps-Universität Marburg he became an associate professor at the Julius-Maximilians-Universität Würzburg (1990). He was a full professor at the Georg-August-Universität Göttingen (1992) and moved to the Albert-Ludwigs-Universität Freiburg in 1998. Being a dedicated teacher, he was a visiting professor at the Universities of Wisconsin / Madison and Santiago de Compostela / Spain. His research interests comprise the synthetic chemistry of dienediynes, 1,3,5,7,...-polyols, chiral butyrolactones and butenolides, and the stereochemistry of rearrangements of organolithium compounds.

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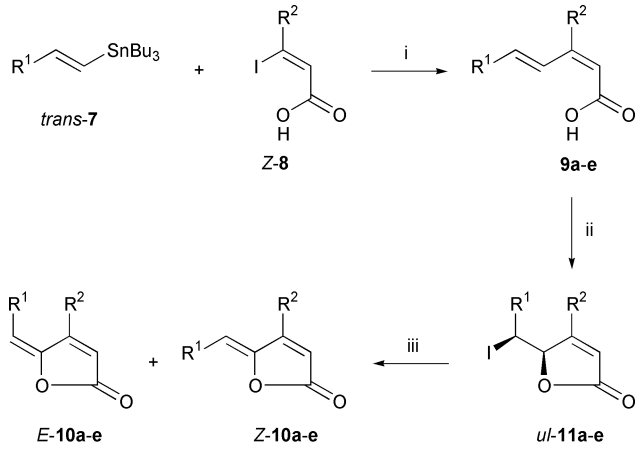
of the present top ten block busters of the pharmaceutical industry effect—namely Lipitor®, Zocor® and Pravachol®. The structurally most complex γ-alkylidenebutenolides of the substitution pattern under scrutiny are the carotinoids peridinin[4] (*Z*-**18a**, Scheme 5) and pyrrhoxanthin[5] (*Z*-**18b**, Scheme 5). Peridinin plays a key role in marine photosynthesis by dinoflagellates, which make up much of the sea plankton. Light harvesting by *Amphidinium carterae* is effected by a chromoprotein whose 2 active centers contain 2 × four molecules of peridinin, 2 × one molecule of chlorophyll A and 2 × one molecule of a (digalactosyl)diacylglycerol.[6] The conversion of light into chemical energy is a fundamentally important process.[7] Pyrrhoxanthin participates in algal photosynthesis.

Each of the γ-alkylidenebutenolides just mentioned has attracted synthetic attention in recent years[8] (Scheme references: *vide supra*), as have several others, too. The latter comprise the goniobutenolides A (*Z*-**27**) and B (*E*-**27**, Schemes 9, 29), the antibiotic lissoclinolide (*trans,Z,trans*-**52**, Scheme 14), the isomeric structure *trans,E,trans*-**52** once assigned to tetrenolin (Scheme 15), constituent *Z*-**72** of the roots of *Chamaemelum nobile* L. (Schemes 19, 22), the alkaloid pandamarilactam-3y (*Z*-**85**, Scheme 23), the cytotoxin nostoclide II (*Z*-**89**, Scheme 24), the wood constituent freelingyne (*Z*-**93**, Scheme 25), melodorinol (*Z*-**99**, Scheme 26), the antibiotic patulin,[9] and an eudesmanolide.[10]

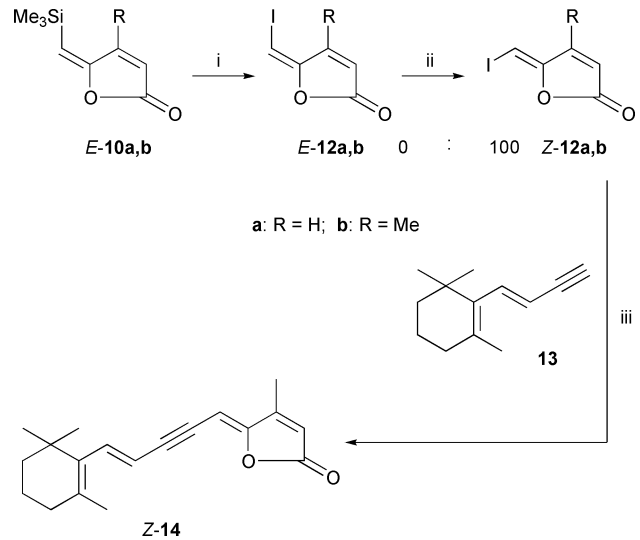
The present article reflects the current interest in the preparation of such compounds.[11] Specifically, it compiles ways of assembling such γ-alkylidenebutenolides by means of



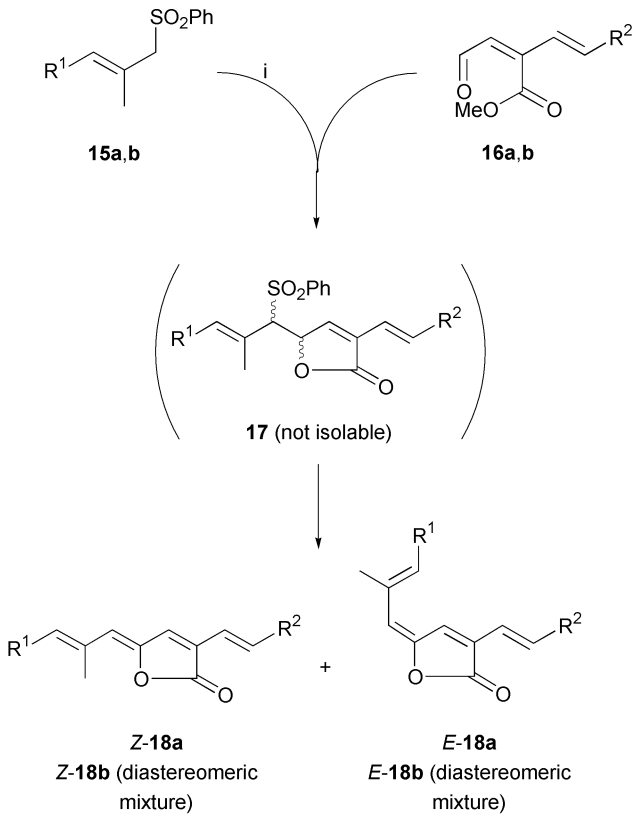
	a	b	c	d	e
R^1	$SiMe_3$	$SiMe_3$	$SiMe_3$	$SiMe_3$	Ph
R^2	H	Me	CH_2OMe	Ph	Me
ii at °C	-78	-78	-78	-78	-30
% Yield **10**	87	85	71	54	70
E : *Z*	99:1[a]	98:2[b]	95:5	46:54	0:100

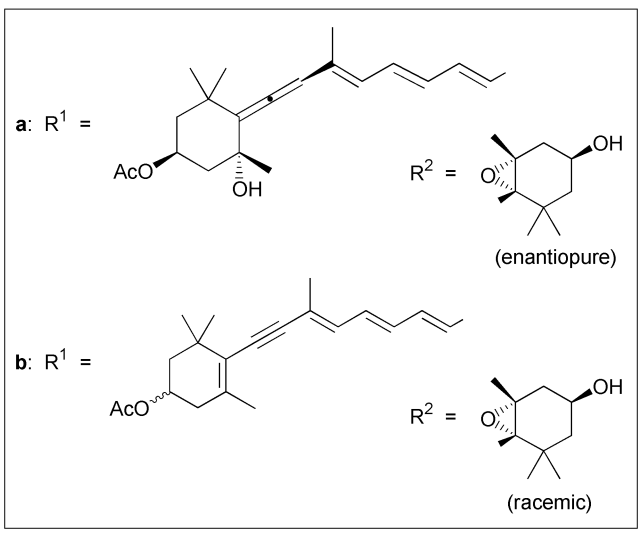
[a]70:30 at 20 °C; [b] 83:17 at -30 °C.

Scheme 3 *Reagents*: i, Stille coupling; ii, either KI, $Na_2S_2O_8$, H_2O, or ICl, CH_2Cl_2, 48–73%; iii, DBU, CH_2Cl_2.



Scheme 4 *Reagents*: i, I_2, AgO_2CCF_3, THF, 'good yield'; ii, Et_2O, 'quantitatively'; iii, for *Z*-**12b**: $Pd(PPh_3)_4$, CuI, $BuNH_2$, benzene, 65%.

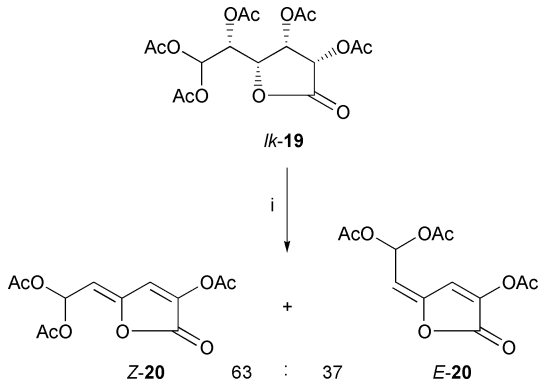




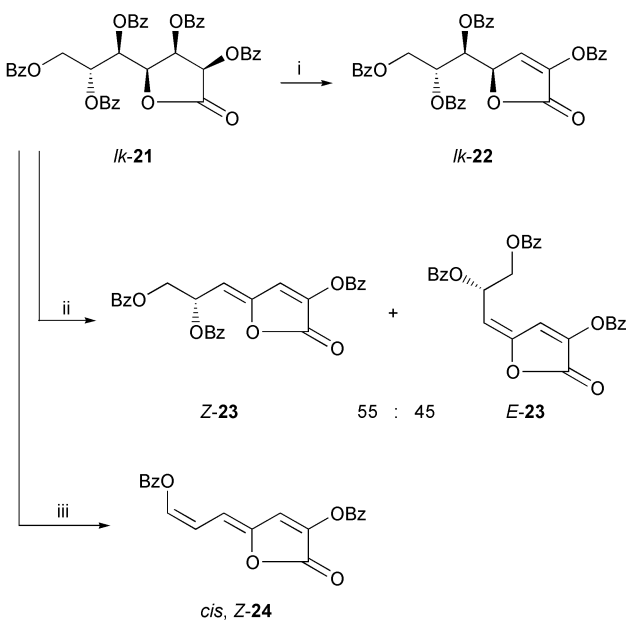
Scheme 5 *Reagents*: i, LDA, THF–hexanes, for **a**: addition of **16a**, *Z*-**18a**:*E*-**18a** mixture: 18% relative to **16a** = 12% relative to **15a**, for **b**: addition of **16b**, *Z*-**18b**:*E*-**18b** mixture after preparative TLC: 13% relative to **16b** = 8.4% relative to **15b**, for **a** and **b**: stereopure products after preparative HPLC, *Z*-**18a**: 2.9% relative to **16a** = 1.9% relative to **15a**, *E*-**18a**: 2.8% relative to **16a** = 1.9% relative to **15a**, *Z*-**18b**: 5.9% relative to **16b** = 3.7% relative to **15b**, *E*-**18b**: 4.9% relative to **16b** = 3.1% relative to **15b**.

the strategy outlined in Scheme 1.[12] Its key step is an *anti*-elimination of a leaving group Het at C$^{\alpha\prime}$ and an adjacent proton at C$^{\gamma}$ from diastereopure γ-(α-heteroalkyl)-substituted butenolides **1**. If the latter possesses stereostructure *lk*-**1**, the *anti*-elimination of α′-Het and γ-H establishes *Z*-configured γ-alkylidenebutenolides *Z*-**2** while the isomeric starting materials *ul*-**1** serve as precursors of the stereocomplementary γ-alkylidenebutenolides *E*-**2**. In order for these eliminations to be stereo*specific*, there must not be competing *syn*-eliminations. Neither may the elimination products *Z*- and *E*-**2** equilibrate under the reaction conditions—*Z*-**2** is slightly or distinctly more stable than *E*-**2**.

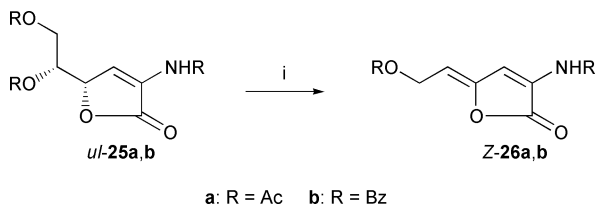
To the best of our knowledge, the earliest realization of a (fairly) *anti*-selective elimination of type *ul*-**1** → *E*-**2** is due to Font *et al*. in 1989.[13] As shown in Scheme 2, the dehydrobromination of the γ-(α-bromoethyl)-substituted butenolide *ul*-**6** with NEt_3 gave a 90 : 10-mixture of *E*- and *Z*-**5**.



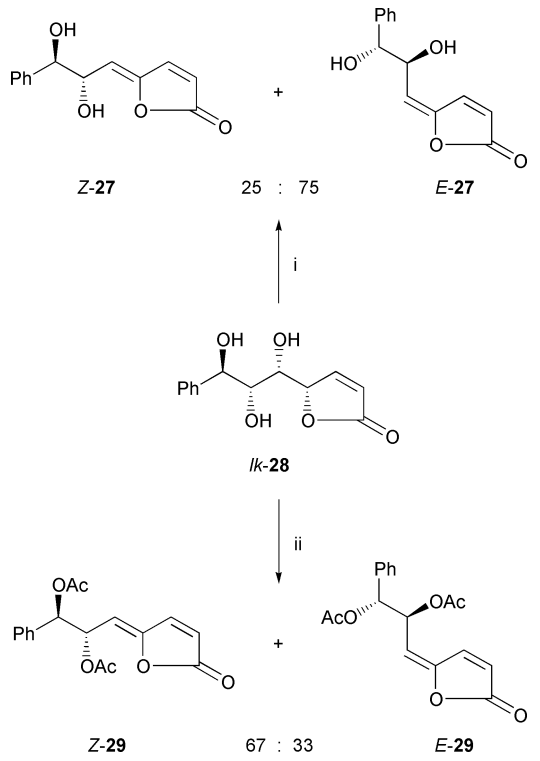
Scheme 6 *Reagents*: i, NEt_3, Ac_2O, 91%.



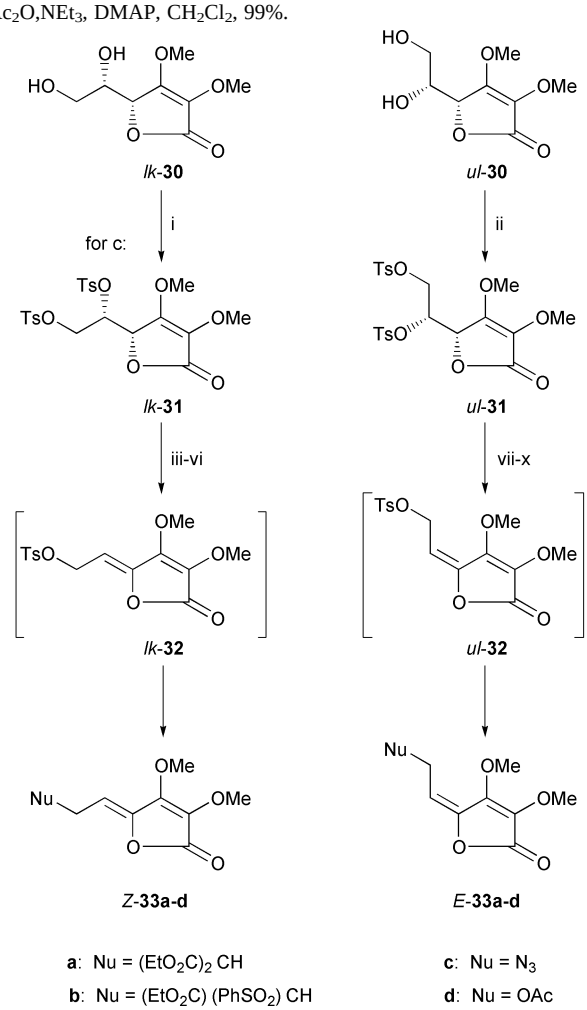
Scheme 7 *Reagents*: i, DBU, CH_2Cl_2, 67%;[18] ii, NEt_3, $CHCl_3$, 85% (experimental part)–90% (according to Scheme);[19] iii, NEt_3–$CHCl_3$, 59%.[20]



Scheme 8 *Reagents*: i, for **a**: DBU, CH_2Cl_2, 71%, for **b**: DBU, CH_2Cl_2, crystallization, 62%.



Scheme 9 *Reagents*: i, $(F_3C–CO)_2O$, NEt_3, CH_2Cl_2, then MeOH, 79%; ii, Ac_2O,NEt_3, DMAP, CH_2Cl_2, 99%.



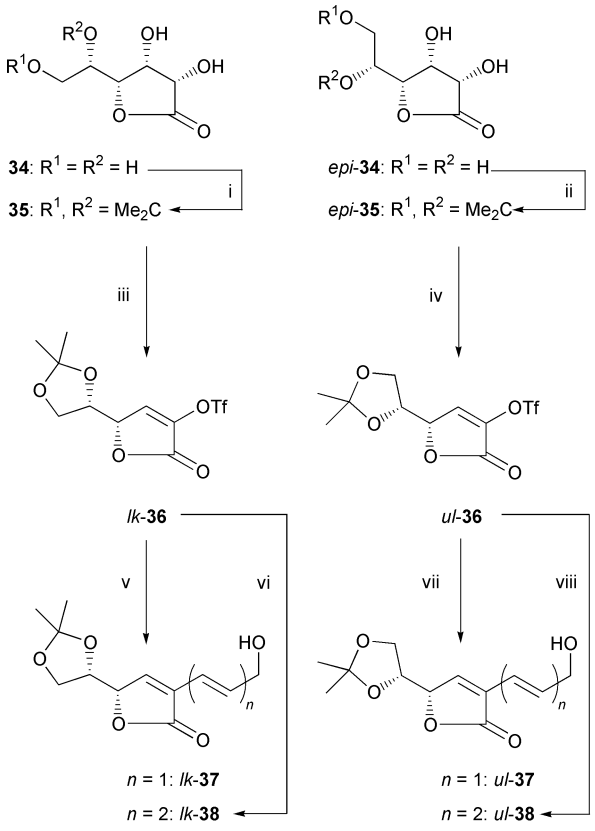
Scheme 10 *Reagents*: i, TsCl, pyridine, 86%; ii, same as (i), 86%; iii, for **a**: $(EtO_2C)_2CH^-Na^+$, THF, 78%; iv, for **b**: $(EtO_2C)(PhSO_2)CH^-Na^+$, THF, 82%; v, for **c**: NaN_3, DMF, 85%; vi, for **d**: NaOAc, DMF, 70%; vii, same as (iii), 70%; viii, same as (iv), 81%; ix, same as (v), 86%; x, same as (vi), 73%.

One must be aware that such an *E*-selectivity can easily be erased by an ensuing (partial or completely) $E \rightarrow Z$ isomerization. This is evidenced, for instance, by the DBU-mediated dehydroiodinations tabulated in Scheme 3.[14] The β-substituents R^2 of elimination products *Z*-**10b**–**e** destabilize the neighboring alkylidene substituents R^1 so much that substrate *ul*-**11e** undergoes a 100% *syn*-selective β-elimination.

Clearly, such a thermodynamically driven $E \rightarrow Z$ isomerization may be exploited for synthesizing *Z*-γ-alkylidenebutenolides selectively. This is underlined by the elaboration of the γ-[(trimethylsilyl)methylene]butenolides *E*-**10a** and **b** shown in Scheme 4.[14] The γ-(iodomethylene)butenolides *E*-**12a** and **b** obtained from these compounds by iodolysis provided the stereopure isomers *Z*-**12a** and **b** within 1 h at room temperature. Compound *Z*-**12b** underwent a Sonogashira–Hagihara coupling with alkyne **13** which proceeded with retention of configuration at the $C^{\alpha'}$=C^{γ} bond and provided the vitamin A lactone analog *Z*-**14** in 65% yield.

The fairly sophisticated β-eliminations of Scheme 5 allowed Ito *et al.* to achieve the first syntheses of the γ-alkylidenebutenolide carotinoids peridinin (*Z*-**18a**) and pyrrhoxanthin (*Z*-**18b**).[15] Benzenesulfonic acid was eliminated from the γ-(α-phenylsulfonyl)-substituted butenolides **17** which were formed *in situ* by the addition of the appropriate lithiated sulfone **15a** or **b** to the respective aldehydoester **16a** or **b**. This addition is expected to lack simple diastereoselectivity—like the first step of the Julia–Lythgoe olefination. Therefore, the corresponding intermediates **17** should arise as *lk*,*ul*-mixtures. The latter circumstance explains, in conjunction with the stereochemical relationships of Scheme 1, why the elimination products **18a** and **b** resulted as *Z*,*E*-*mixtures*.

One concludes that *stereospecific* β-elimination routes to γ-alkylidenebutenolides depend on the availability of diastereopure *lk*- and *ul*-configured γ-(α-heteroalkyl)-substituted butenolides **1**. These compounds have been prepared successfully from sugars, by (Mukaiyama) aldol additions, and by the route of Scheme 30, as specified in the following sections.

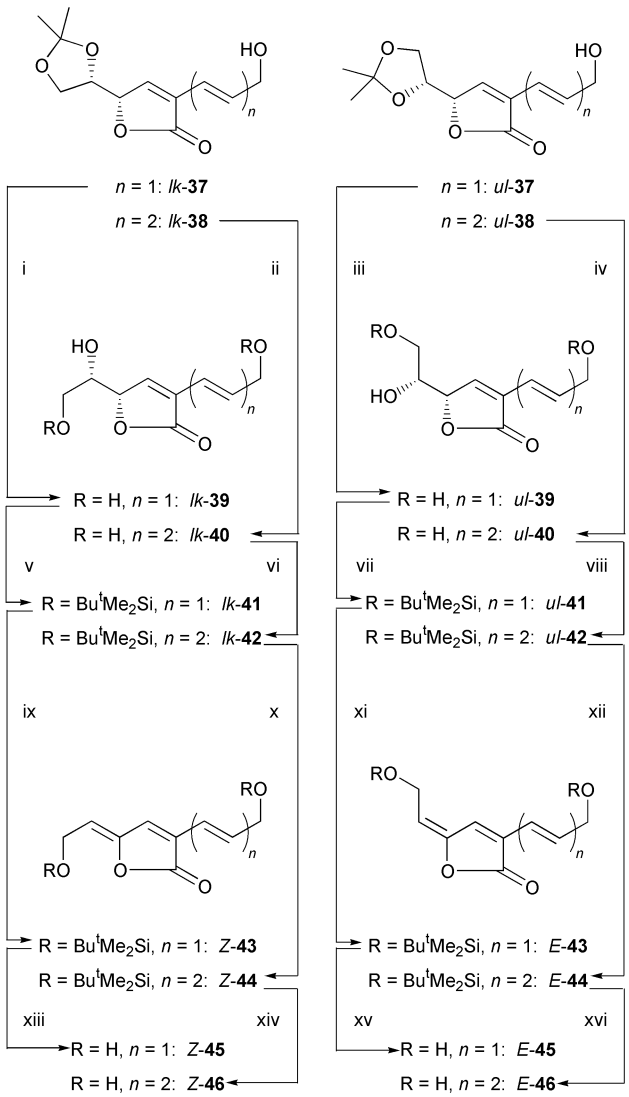


Scheme 11[24] *Reagents*: i, 2,2-Dimethoxypropane Amberlyst-15, DMF, 68% (ref. 25 60%, ref. 26 70%); ii, same as (i), 74% (ref. 25 77%); iii triflic anhydride, pyridine (4.0 equiv.), CH_2Cl_2, 74% (ref. 27 70%); iv, same as (iii), 70% (ref. 27 74%); v, *trans*-3-(tributylstannyl)prop-2-en-1-ol, $Pd_2(dba)_3$·$CHCl_3$, $AsPh_3$, LiCl, THF, 78%; vi, *trans*,*trans*-5-(tributylstannyl)penta-2,4-dien-1-ol, $Pd_2(dba)_3$·$CHCl_3$, $AsPh_3$, LiCl, THF, 57%; vii, same as (v), 68%; viii, same as (vi), 75%.

β-Eliminations from sugar lactones[16]

D-Glucurolactone and acetyl chloride react to give the saturated lactone *lk*-**19** shown in Scheme 6. Treatment with triethylamine in acetic anhydride induced two β-eliminations.[17] First, the C^{α}=C^{β} bond formed, as inferred from the analogous conversion *lk*-**21** → *lk*-**22** in Scheme 7.[18] Then, the $C^{\alpha'}$=C^{γ} bond was established. 57% of the *Z*-configured and 34% of the *E*-configured γ-alkylidenebutenolide **20** resulted,[17] *i.e.* the second elimination was non-stereoselective.

In a similar manner, the perbenzoate *lk*-**21** of D-seduheptulonolactone and triethylamine undergo multiple β-eliminations (Scheme 7).[18–20] As in the case of Scheme 6, the second elimination lacks stereocontrol since the γ-alkylidenebutenolide **23** forms as a 55 : 45 mixture of *anti*-elimination product *Z*-**23** and *syn*-elimination product *E*-**23**.[19] By a 10-fold increase of the reaction time, a third elimination of benzoic acid ensued. It



Scheme 12[24] *Reagents*: i, HCl (12 M), CH_2Cl_2, MeOH, 78%; ii, same as (i), 73%; iii, same as (i), 65%; iv, same as (i), 71%; v, Bu^tMe_2SiCl, imidazole, molecular sieves 4 Å, DMF, 73%; vi, same as (v), 48%; vii, same as (v), 70%; viii, same as (v), 51%; ix, triflic anhydride, pyridine, CH_2Cl_2, 81% of a 99 : 1 *Z*-**43** : *E*-**43** mixture; x, same as (ix), 69% of a 97 : 3 *Z*-**44** : *E*-**44** mixture; xi, same as (ix), 63% of a 96 : 4 *E*-**43** : *Z*-**43** mixture; xii, same as (ix), 73% of a 97 : 3 *E*-**44** : *Z*-**44** mixture; xiii, HF·pyridine, THF, 96% of a 94 : 6 *Z*-**45** : *E*-**45** mixture; xiv, same as (xiii), 92% of diastereopure *Z*-**46**; xv, same as (xiii), 86% of a 94 : 6 *E*-**45** : *Z*-**45** mixture; xvi, same as (xiii), 96% of a 95 : 5 *E*-**46** : *Z*-**46** mixture.

created the conjugated γ-alkylidenebutenolide **24** as a pure *cis*,*Z*-isomer.[20] Since the yield of this compound measured 60–80%, the $C^{\alpha'}$=C^{γ} bond of its precursor **23** (55 : 45 *Z* : *E* mixture, 85–90% yield if isolated) must have partly reverted to the *Z*-geometry under the influence of thermodynamic control.

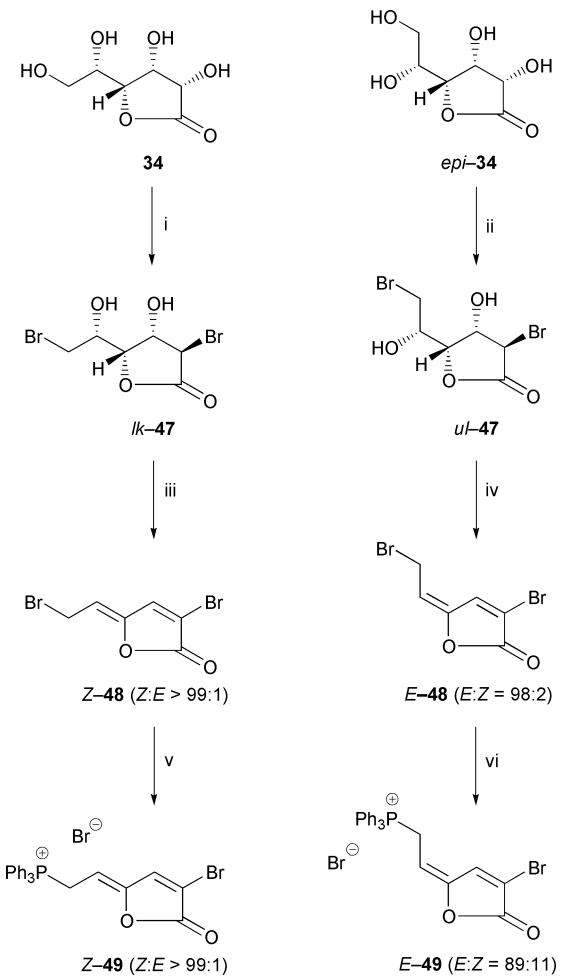
Thermodynamic control must also be responsible for the *syn*(!)-preference of the related, DBU-driven β-eliminations of acetic or benzoic acid from the acylamino-substituted sugar lactones *ul*-**25a** and **b**, respectively (Scheme 8).[21]

Why triethylamine and the tris(trifluoroacetate) derived from the butenolide *lk*-**28** shown in Scheme 9 give a 1 : 3 ratio of *anti*- and *syn*-elimination, while the analogous triacetate does so in a 2 : 1 ratio, is difficult to rationalize.[22] But clearly, the findings of Schemes 6–9 suggest that in γ-(α-heteroalkyl)-substituted butenolides which are to undergo a selective *anti*-elimination and provide sterically homogenous γ-alkylidenebutenolides thereby, the leaving group should *not* be a carboxylic acid. Presumably, a *better* leaving group is called for.

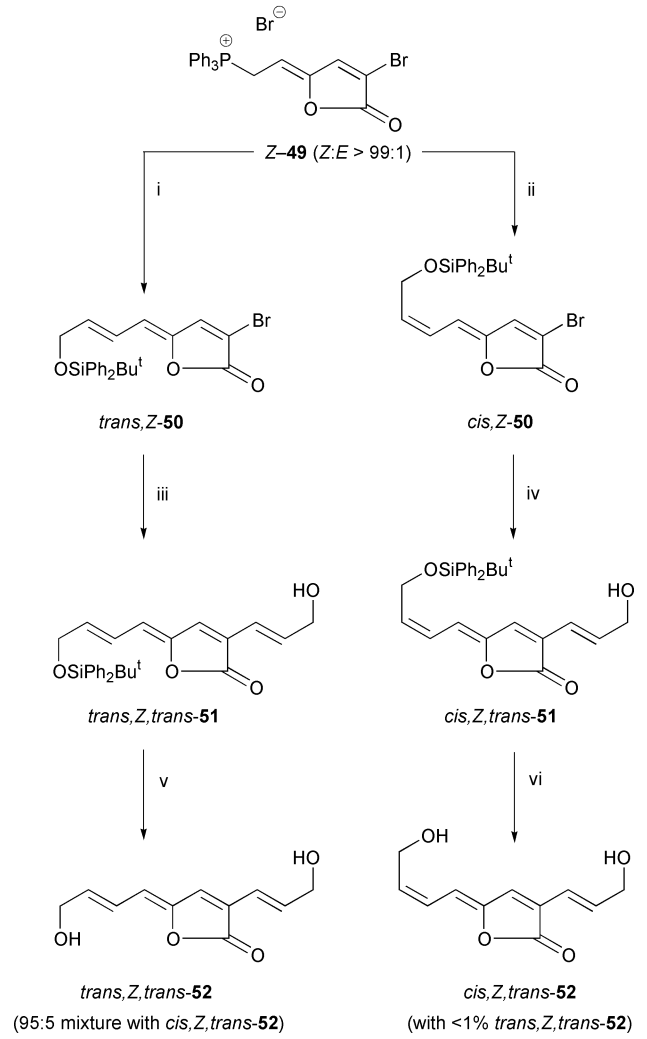
This thought represented *our* start into γ-alkylidenebutenolide syntheses.[12] However, it had already been considered by Khan and Adams in 1995 when they published the study displayed in Scheme 10.[23] The starting materials of these authors were two readily accessible sugar lactones, namely the dimethyl ether *lk*-**30** of L-ascorbic acid and the dimethyl ether *ul*-**30** of D-isoascorbic acid. Treatment of these species with tosyl chloride at room temperature in pyridine provided the diastereomeric ditosylates *lk*-**31** and *ul*-**31**, respectively, both in 86% yield. At 60–80 °C, these compounds became elimination substrates upon treatment with a variety of reagents acting as bases and nucleophiles simultaneously. Behaving as bases, they induced highly stereoselective *anti*-eliminations of toluene-*p*-sulfonic acid which established the homogeneously configured $C^{\alpha'}$=C^{γ} bonds of the presumed intermediates *lk*-**32** and *ul*-**32**, respectively. Then, the same reagents substituted the allylic tosyloxy group nucleophilically: 70–86% of the pure *Z*- and *E*-isomers of the γ-alkylidenebutenolides **33a**–**d** resulted.

Khan's and Adams' results encouraged us to develop *our* β-elimination route[12,24] from sugar lactones to stereodefined γ-alkylidenebutenolides (Schemes 11–17). Clearly, we felt more strongly their message 'this route in principle should work' than we anticipated how profoundly differently our materials behaved in comparison to theirs. We were to deal with 'true' α,β-unsaturated lactones while they had used α,β-unsaturated lactones, which, constituting vinylogous carbonates, are resonance-stabilized. Accordingly, none of our γ-alkylidenebutenolides could be heated overnight at 60–80 °C like theirs (*vide supra*) without suffering decomposition, not to speak of undergoing extensive *E*–*Z*-isomerization much earlier. Indeed, in each step following the installment of the crucial $C^{\alpha'}$=C^{γ} bond skillful experimentation was called for in our work lest the $C^{\alpha'}$=C^{γ} bond geometry be eroded.

Our methodology study (Scheme 11[24]) started from the hydrogenation products **34** ('L-gulonolactone') of L-ascorbic acid and *epi*-**34** ('D-mannonolactone') of D-isoascorbic acid. Acetonide formation, bis(triflate) formation, and *in situ* β-elimination furnished the butenolide-based enol triflates *lk*- and *ul*-**36**, respectively, as described earlier.[27] In the presence of 2 mol% $Pd_2(dba)_3$·$CHCl_3$, $AsPh_3$ and LiCl, these compounds underwent smooth Stille couplings with *trans*-3-(tributyl-



Scheme 13[28] *Reagents*: i, HBr, HOAc, afterwards addition of MeOH, 78% (ref. 29: 90%); ii, same as (i), 71% (ref. 30: 63%); iii, Tf_2O, pyridine, CH_2Cl_2, 95%; iv, same as (iii), 63%; v, Ph_3P, acetonitrile, 96%; vi, same as (v), 80%.



Scheme 14 *Reagents*: i, LDA, THF, $Bu^tPh_2SiOCH_2$–CH=O, −78 °C → 60 °C, 93%; ii, same as (i) but −78 °C → 25 °C, 72%; iii, *trans*-Bu_3Sn–CH=CH–CH_2OH, Pd_2dba_3·$CHCl_3$, $AsPh_3$, THF, 74%; iv, same as (iii), 78%; v, HF·pyridine, THF, 81%; vi, same as (v), 84%.

stannyl)prop-2-en-1-ol and *trans,trans*-5-(tributylstannyl)-penta-2,4-dien-1-ol. The α-alkenylated butenolides **37** and **38** resulted. They were liberated from their acetonide groups, furnishing the triols **39** and **40**, respectively (Scheme 12[24]). After selective *tert*-butyldimethylsilylation of their primary OH groups, the remaining secondary OH group of compounds **41** and **42** was poised to undergo the desired *anti*-elimination after activation with triflic anhydride. Pyridine accomplished this task at −25 °C. The α-alkenyl-γ-alkylidenebutenolides **45** and **46** resulted in 86–96% yield. Their isomeric purities were *Z*:*E* = 94:6 or 6:94 in the former case and *Z*:*E* = 100:0 or 5:95 in the latter. The viability of our strategy had thereby been demonstrated.

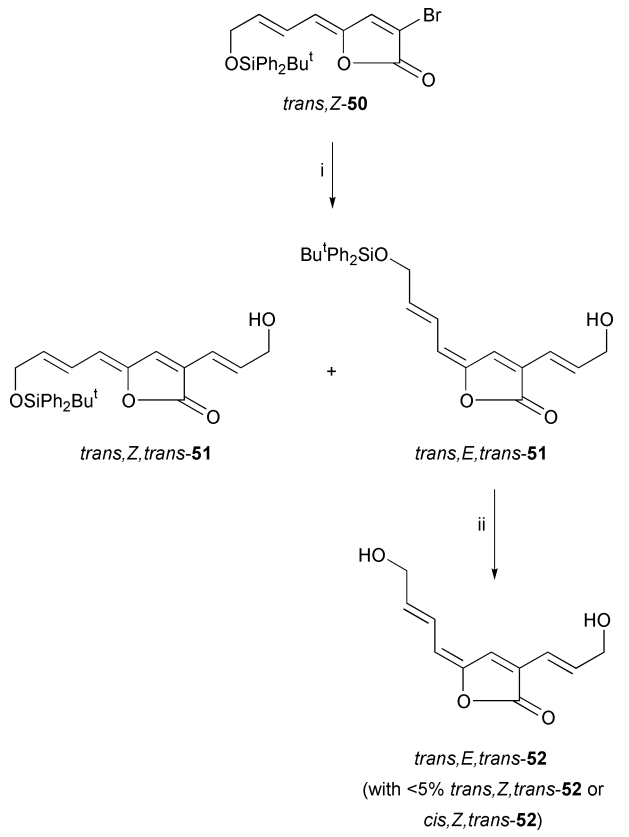
In two other sequences, the known[29,30] twofold S_N2-attack of HBr upon the primary and the activated secondary OH group of lactones **34** and *epi*-**34** delivered the dibromodihydroxylactones *lk*- and *ul*-**47** selectively (Scheme 13). Bistriflate formation in the presence of pyridine made possible two β-eliminations. They led to the bromine-containing γ-alkylidenebutenolides *Z*- and *E*-**48** as almost pure diastereomers. Allylic substitution by triphenylphosphine gave the corresponding phosphonium salts **49** with complete retention of the *Z*- and partial loss of the *E*-geometry.

The ylide derived from phosphonium salt *Z*-**49** reacted with $Bu^tPh_2SiOCH_2$–CH=O with complete retention of the $C^{\alpha'}$=Cγ bond geometry (Scheme 14[28]). The newly formed $C^{\beta'}$ = Cγ′ bond of olefination product **50** was either *trans*- or *cis*-configured, depending on whether the Wittig reaction was conducted at 60 or 25 °C. The bromoethylene moiety of the respective product *trans,Z*- or *cis,Z*-**50** could be coupled with *trans*-Bu_3Sn–CH=CH–CH_2OH in the presence of catalytic Pd_2dba_3·$CHCl_3$ and $AsPh_3$. All C=C bonds maintained their configurations under these conditions and did so, too, in the terminating desilylation step. It rendered, in the *trans,Z,trans*-series, the γ-alkylidenebutenolide *trans,Z-trans*-**52**, which had been described as the antibiotic lissoclinolide. This was the third and is the hitherto shortest synthesis of this compound. Two entirely different syntheses of lissoclinolide had been realized shortly before in the laboratories of Rossi[31] and Negishi.[32]

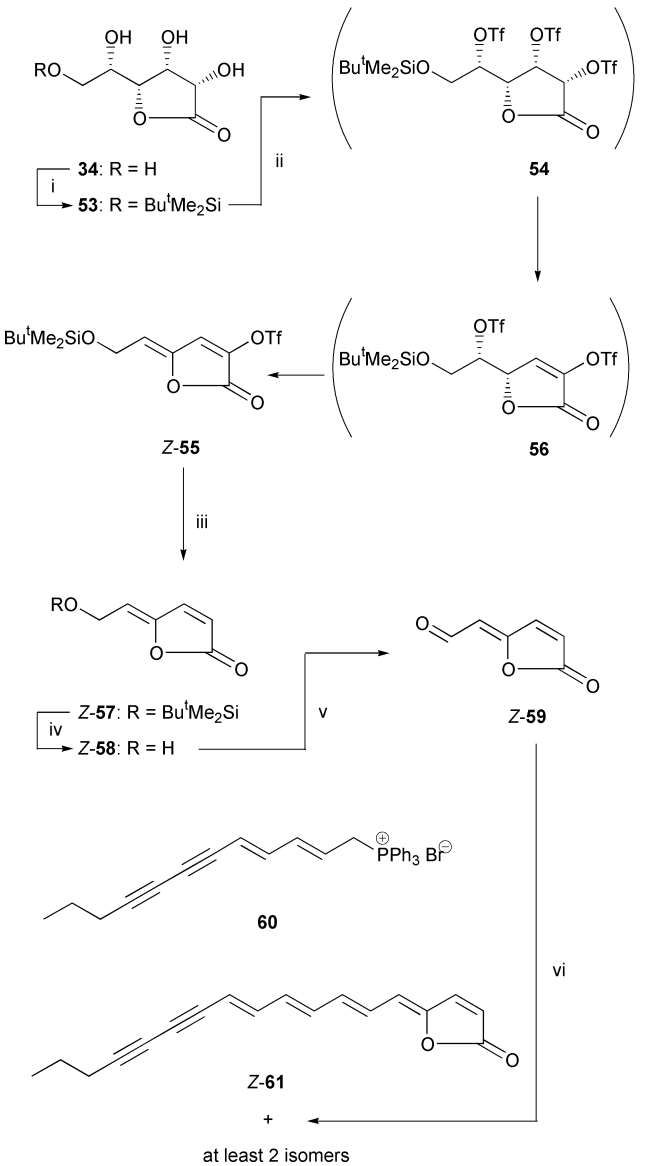
Disappointingly, the ylide derived from phosphonium salt *E*-**49** reacted with $Bu^tPh_2SiOCH_2$–CH=O with complete inversion of the $C^{\alpha'}$=Cγ bond geometry,[28] *i.e.* providing the same *Z*-configured condensation products *trans,Z*-**50** or *cis,Z*-**50** which we had already prepared starting from the isomeric phosphonium salt *Z*-**49** (Scheme 14). This means that the ylide in question underwent a thermodynamically driven *E*→ *Z*-isomerization.

Scheme 15 shows how we managed to get at least small amounts of the Stille coupling product *trans,E,trans*-**51** (which our Wittig approach had failed to give) from the bromoolefin precursor *trans,E*-**50** by a partial isomerization of the previously obtained (*cf.* Scheme 14) coupling product *trans,Z,trans*-**51**. A subsequent desilylation furnished isomer *trans,E,trans*-**52** of lissoclinolide (*trans,Z,trans*-**51**). This isomer was until then suspected to represent 'tetrenolin'.[33] However, having both isomers at hand, we proved by ^{1}H-NMR spectroscopy that "tetrenolin" possesses the structure of lissoclinolide.

Scheme 16 shows the first synthesis of dihydroxerulin (*Z*-**61**).[34] It allowed us to assign a *trans*-configuration to the C=C

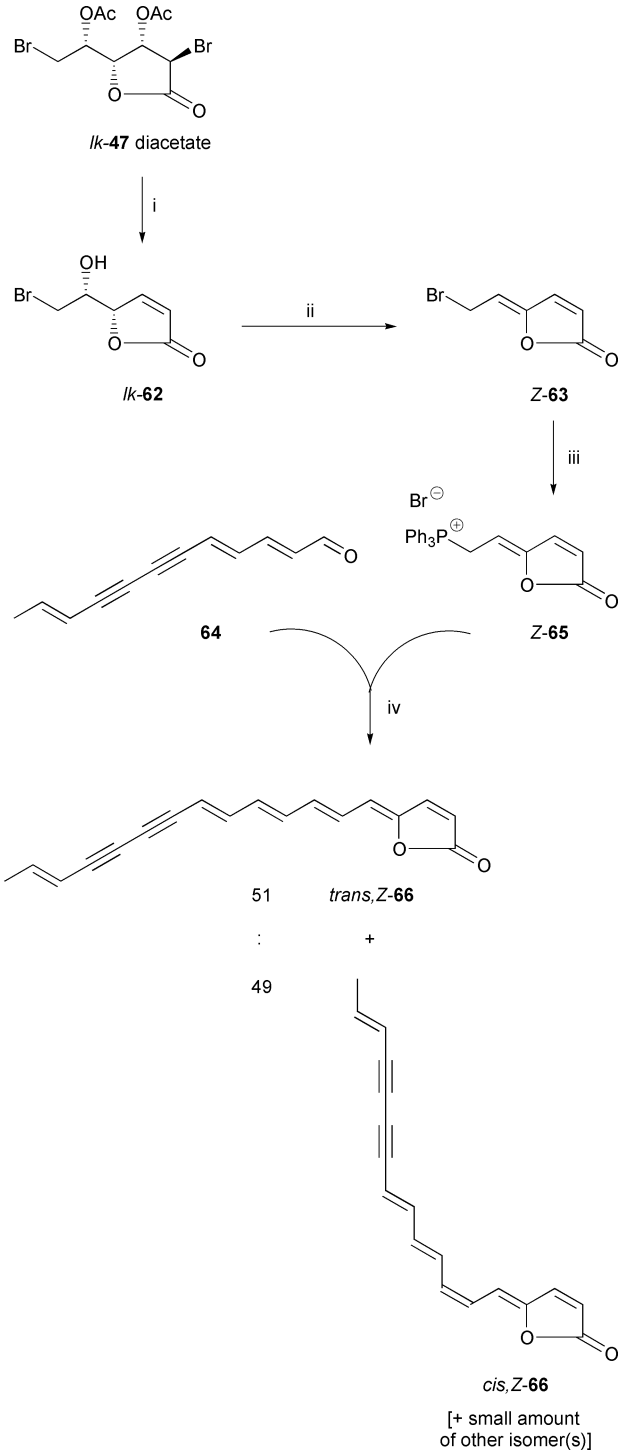


Scheme 15[28] *Reagents*: i, *trans*-Bu_3Sn–CH=CH–CH_2OH, Pd_2dba_3·$CHCl_3$, $AsPh_3$, THF, 71% *trans,Z,trans*-**51** + 20% *trans,E,trans*-**51**; ii, HF·pyridine, THF, 89%.



Scheme 16[34] *Reagents*: i, Bu^tMe_2SiCl, imidazole, DMF, 58%; ii, pyridine, triflic anhydride, CH_2Cl_2, 78% (*Z*:*E* > 99:1); iii, LiCl, $NiCl_2(PPh_3)_2$, THF, Bu_3SnH, 83% (*Z*:*E* = 94:6); iv, HF·pyridine, THF, 80% (*Z*:*E* = 96:4); v, Dess-Martin periodinane, CH_2Cl_2, 90% as a 95:5-mixture, recrystallized as a 98:2 *Z*:*E* mixture, 82%; vi, **60**, *n*BuLi, THF, *Z*-**59**, after repeated chromatographies 30% *Z*-**61** and 25% mixture of other isomers.

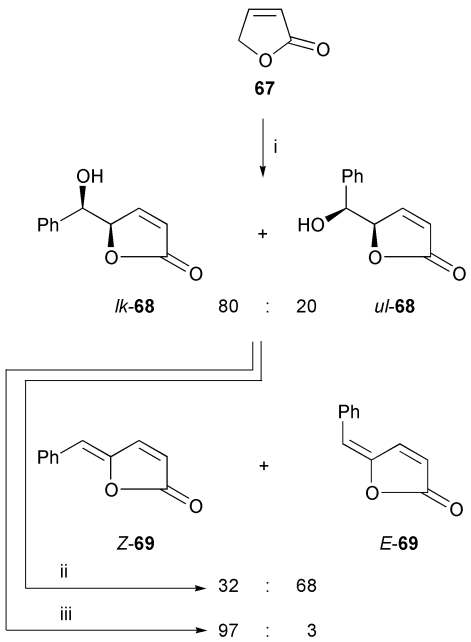
bond which could not be assigned by the spectroscopic study of the natural specimen[3] because of signal overlap with contaminating xerulin (*trans*,*Z*-**66**, Scheme 17). A conceptionally different synthesis of dihydroxerulin has since been elaborated by Rossi *et al*.[35] Initially, we sulfonylated the three OH groups of the O_{prim}-*tert*-butyldimethylsilyl protected L-gulonolactone **53** with triflic anhydride. The resulting tristriflate **54** underwent two *in situ* β-eliminations of triflic acid, the first elimination rendering butenolide **56**, the second leading to the isomerically pure alkylidenebutenolide *Z*-**55**. The enol triflate moiety of this compound was hydrogenolyzed readily to give lactone *Z*-**57** in the presence of catalytic $NiCl_2(PPh_3)_2$ and stoichiometric Bu_3SnH. A Wittig reaction of the derived aldehyde *Z*-**59** with



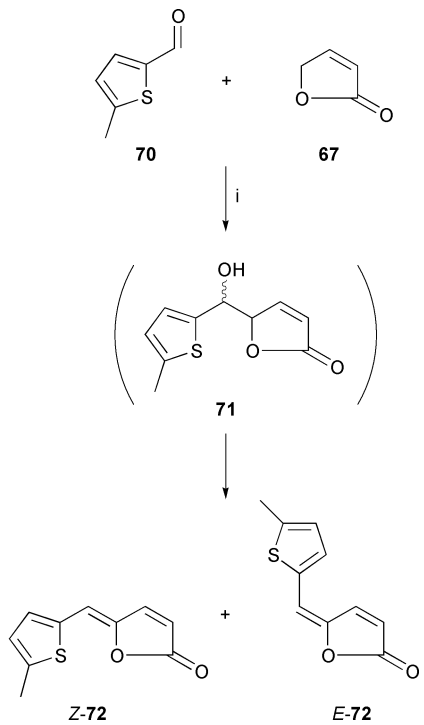
Scheme 17[36] *Reagents*: i, Na_2SO_3, $NaHSO_3$, MeOH, H_2O, crude product treated with MeOH–HCl, 92% overall (ref. 37: 64%); ii, triflic anhydride, pyridine, CH_2Cl_2, 63% (*Z*:*E* 97:3); iii, PPh_3, H_3C–CN, 100%; iv, K_2CO_3, **64**:*Z*-**65** 11:2, CH_2Cl_2, 28% *trans*,*Z*-**66** + 27% [*cis*,*Z*-**66** + small amount of isomer(s)].

the ylide corresponding to the phosphonium salt **60** followed but, unfortunately, exhibited no stereocontrol: it delivered 30% dihydroxerulin *Z*-**61** and 25% of at least two isomers. Yet, this synthesis encompasses only 2 × 5 consecutive steps in the linear sequences and a final converging step.

The first synthesis of xerulin (*trans*,*Z*-**66**) was also effected by our β-elimination strategy (Scheme 17).[36] We started with the diacetate of dibromolactone *lk*-**47** (preparation:[29,30] Scheme 13). A reductive elimination[37] established the $C^{\alpha}=C^{\beta}$ bond of butenolide *lk*-**62** and a subsequent base-promoted elimination the $C^{\alpha'}=C^{\gamma}$ bond of the γ-alkylidenebutenolide **63** (97% *Z*). An S_N2 reaction of this compound with triphenylphosphine provided the corresponding phosphonium salt **65** (96% *Z*). The terminating reaction of Scheme 17 was a Wittig olefination. It showed no more stereocontrol than the Wittig reaction of



Scheme 18[40] *Reagents*: i, LDA, THF, Ph–CH=O, 76%; ii, MsCl, pyridine, 0 °C → 80–90 °C, 87%; iii, same as (ii) but only rt, 96%.

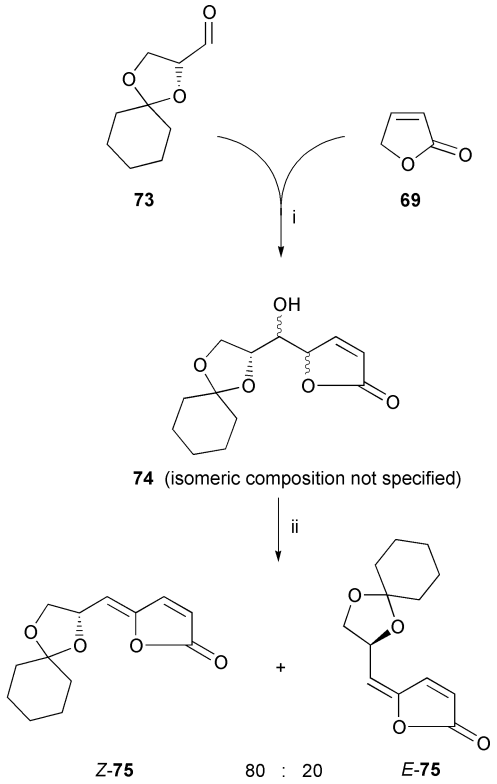


Scheme 19[41] *Reagents*: i, **70**:**67** 1:1, piperidinium acetate, HOAc, 36%.

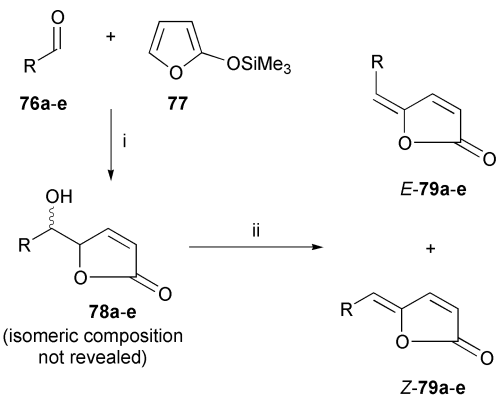
opposite polarity used for synthesizing dihydroxerulin (*Z*-**61**; Scheme 16). Thus, it furnished equal, but separable, amounts of xerulin (*trans,Z*-**66**; 28% yield) and its isomer *cis,Z*-**66**. The recently published, differently tailored synthesis of xerulin by Negishi *et al*. is free from such a drawback.[38]

β-Eliminations from (Mukaiyama) aldol adducts

Aldol additions of type-**67** butenolides, *via* their quantitatively derived enolate (Schemes 18, 20) or *via* an equilibrium fraction of the same kind of enolate (Scheme 19), as well as the more widely used Mukaiyama aldol additions of the corresponding



Scheme 20[42] *Reagents*: i, LDA, THF, **73**; ii, crude product from step (i), MsCl, pyridine, 31%.



	a	b	c	d	e
R	Pr−C≡C	Ph	Pent	Ph-CH_2-CH_2	
% Yield **78**	70	95	94	90	92
% Yield **79**	90	91	94	96	92
E:*Z*	5:2	1:1	1:1	3:5	1:1

Scheme 21[43] *Reagents*: i, **76a**–**e**:**77** 1:1.2, $SnCl_4$, CH_2Cl_2, aqueous HCl; ii, Ac_2O, NEt_3, 4-pyrrolidinopyridine, CH_2Cl_2.

siloxyfurans (Schemes 21–25, 27–29) constitute versatile preparations of γ-(α-heteroalkyl)-substituted butenolides **1**. The addition of 5-lithio-2-(*tert*-butoxy)furans to an aldehyde followed by hydrolysis of the resulting heterocycle provides an altervative for attaining the same goal (Scheme 26).

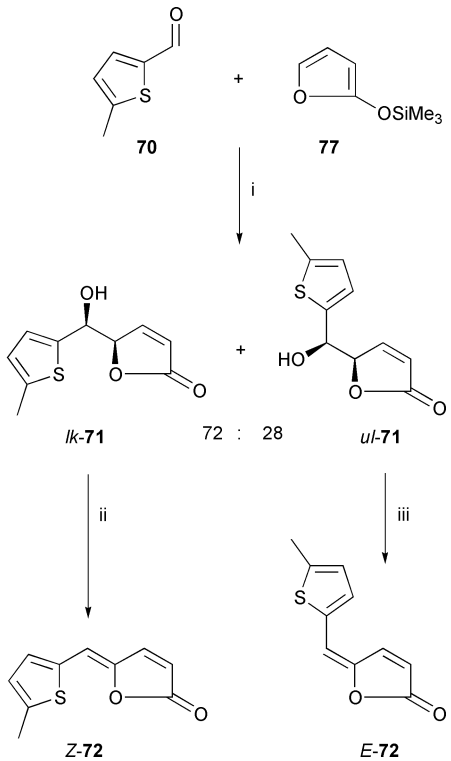
In general, a high degree of simple diastereoselectivity in such aldol additions is limited to the use of α-chiral aldehydes (where *lk*-selectivity of Mukaiyama aldol additions occurs[39]) whereas achiral aldehydes usually show little simple diastereoselectivity. Accordingly, the aldol additions shown in Schemes 18–21 provided the aldol addition products **68**, **71** (formed *in situ*, not isolated), **74** and **79** as *lk,ul-mixtures*. Not having separated them, the subsequent *stereoselective* formation of a γ-alkylidenebutenolide was observed in a single case (*lk*-/*ul*-**68** + mesyl chloride–pyridine → *Z*-**69**; Scheme 18) where thermodynamic control was achieved.

A somewhat related *Z*-preference occurred during the deketalization of the γ-alkylidenebutenolides *Z*- and *E*-**75** of Scheme 20: *Z*-**75** underwent this reaction with complete retention of configuration while *E*-**75** exhibited some *E*→*Z*-isomerization.

If the diastereomeric mixtures of (Mukaiyama) aldol addition products initially obtained are separated, the resulting *lk*-isomer, through an *anti*-elimination, gives a *Z*-configured alkylidenebutenolide and the *ul*-isomer, the *E*-alkylidenebutenolide. Thus, treatment of the thiophene-containing Mukaiyama products *lk*- and *ul*-**71** with Tf_2O and pyridine in dichloromethane provided the alkylidenebutenolides *Z*- and *E*-**72** as single isomers in 67 and 70% yield, respectively (Scheme 22). *Z*-**72** is a constituent of the roots of *Chamaemelum nobile* L.

The pyrrolidone-containing Mukaiyama product *lk*-**84** and an excess of both diethyl azodicarboxylate and PPh_3 gave the isomerically pure *Z*-configured alkylidenebutenolide pandamarilactam-3y *Z*-**85** (Scheme 23). It is noteworthy that the BF_3-promoted aldol addition leading to substrate *lk*-**84** was fairly diastereoselective starting from the (trimethylsiloxy)furan **81** (→ *lk*:*ul* = 88:12) and very diastereoselective starting from the (*tert*-butyldimethylsiloxy)furan **82** (→ *lk*:*ul* = 97:3).

The terminating elimination **88**→**89** in the synthesis of the γ-alkylidenebutenolide nostoclide II (*Z*-**89**, Scheme 24) was also



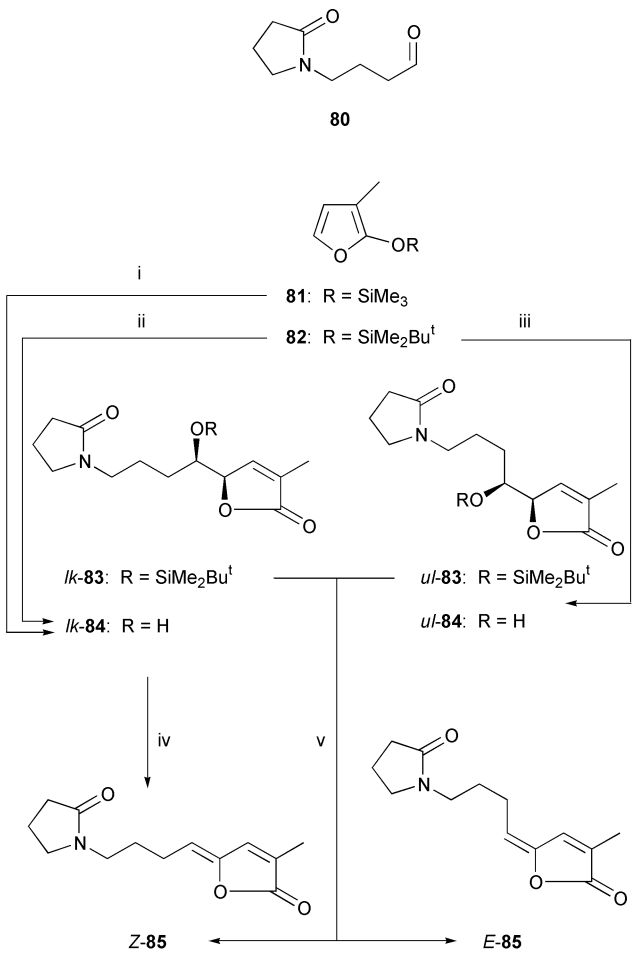
Scheme 22[44] *Reagents*: i, BF_3·OEt_2, aldehyde, CH_2Cl_2, 40%; ii, pyridine, CH_2Cl_2, triflic anhydride, 67%, *Z*-**72**:*E*-**72** 100:0; iii, same as (ii), 70%, *E*-**72**:*Z*-**72** > 99:1.

Z-selective, even when substrate **88** was a mixture (73 : 27) of *lk*- and *ul*-isomers. Probably, *E*-**89** is sterically too hindered to be formed under the reaction conditions (DBU, reflux temperature in chloroform).

Various (trimethylsiloxy)furans and β-iodomethacrolein (**90**) undergo Mukaiyama additions with much more diastereocontrol than simpler α,β-unsaturated aldehydes (*e.g.* crotonaldehyde, cinnamic aldehyde). In the presence of BF_3 etherate, (trimethylsiloxy)furans like compound **81** add to β-iodomethacrolein with > 99% *lk*-selectivity to furnish compounds like *lk*-**91**. Using $ZnBr_2$ as a promoter, the same reactants display an opposite 87 : 13 *ul*-preference. This also makes compound *ul*-**91** accessible as a single isomer (after chromatographic separation). Each of the aldol adducts *lk*- and *ul*-**91** was coupled with 3-ethynylfuran under Pd(0) catalysis (→ *lk*- and *ul*-**92**, respectively).

To our consternation, the *anti*-eliminations *lk*-**92** → *Z*-**93** and *ul*-**92** → *E*-**93** did not yield even trace amounts of product when tried with the elsewhere successful triflic anhydride–pyridine mixture. On the other hand, eliminations with excess diethyl azodicarboxylate–excess PPh_3[48] were high-yielding (94% *Z*-**93**, 87% *E*-**93**) and *anti*-selective. Thus, natural freelingyne (*Z*-**93**) resulted as a 92 : 8 *Z* : *E*- and the unnatural isomer *E*-**93** as a 98 : 2 *E* : *Z*-mixture. Two other stereoselective syntheses of freelingyne are known. They stem from Katsumura *et al.*[49] and Negishi and Liu[50] and are based upon the palladolactonization of a C≡C-containing carboxylic acid followed by a protonolysis of the resulting palladium–carbon bond.

The γ-alkylidenebutenolide syntheses compiled in Schemes 26–29 differ from those collected in Schemes 18–25 since now the $C^{\alpha'}$=C^{γ} bonds are formed through Brønsted (TsOH, HOAc/Δ) or Lewis acid (AgF) mediated β-eliminations. Using the Mukaiyama precursors as diastereomeric mixtures, only the E1-like elimination/fragmentation **96** → *Z*-**97** (Scheme 26) was selective. It furnished, through a subsequent benzoylation, melodorinol (*Z*-**99**).

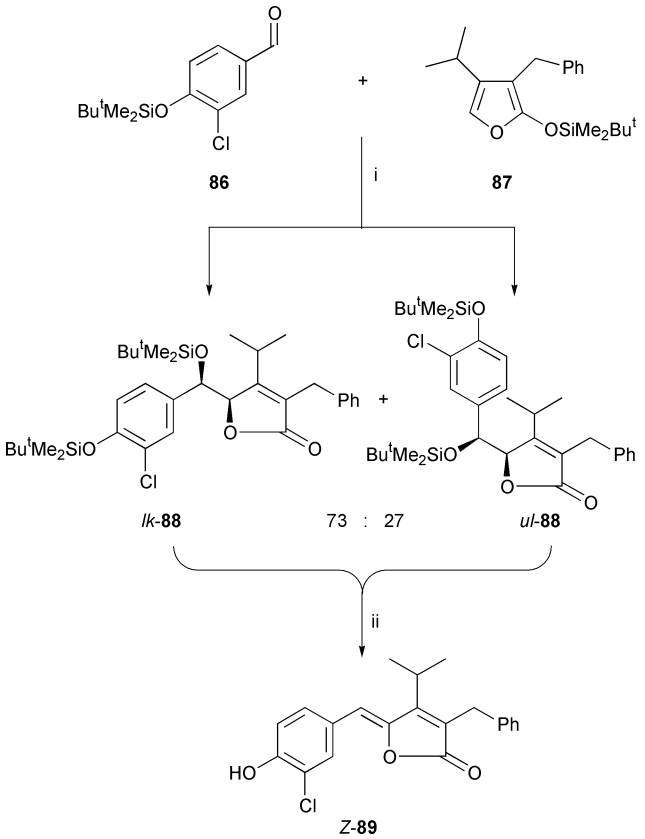


Scheme 23[45] *Reagents*: i, **80**, BF_3·OEt_2, 80% (*lk*-**84** : *ul*-**84** = 88 : 12); ii, **80**, BF_3·OEt_2, 48% **84** (*lk*-**84** : *ul*-**84** = 97 : 3) + 20% recovered **80**; iii, **80**, $Bu_4N^+F^-$ (10 mol%), Bu^tMe_2SiOTf, 37% **83** (*ul*-**83** : *lk*-**83** = 70 : 30) + 11% **84** (*ul*-**84** : *lk*-**84** = 70 : 30); iv, diethyl azodicarboxylate, PPh_3, 82%; v, DBU, 92% (*Z*-**85** : *E*-**85** = 90 : 10).

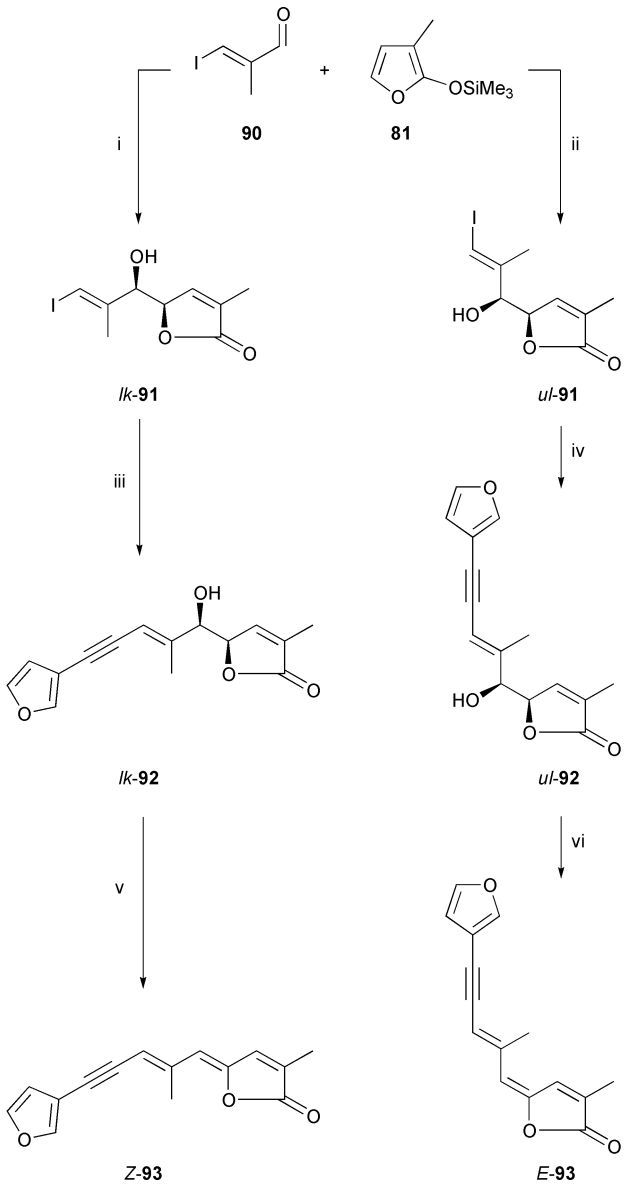
β-Elimination from a differently prepared γ-(α-hydroxyalkyl)butenolide

Our most recent approach to alkylidenebutenolides is presented in Scheme 30.[54] It is conceptually novel, remarkably stereoselective and, as far as the variablity of the substituents is concerned, potentially versatile. Therefore, it looks promising for an analogously shaped synthesis of peridinin (*Z*-**18a**). The latter is currently being pursued in these laboratories in collaboration with Professor de Lera (Universidade de Vigo, Spain). Peridinin plays a key role in the photosynthesis of marine algae.[6]

The starting point of Scheme 30 is the racemic trihalodiene **109**. So far, its 8-step synthesis[54] from the iodomethacrolein **90** is superior to potential short-cuts. Compound **109** was elaborated with a high degree of regio- and stereocontrol into the target butenolide **116**. First, it underwent a selective Suzuki coupling with the phenyl-substituted vinylboronic acid **110** at the less hindered C=C(–H)–I terminus—for steric and bond-energy reasons. Monocoupling product **111** was isolated in 56% yield. Under the same conditions, but using only 3% $Pd(PPh_3)_4$ rather than 5% as previously, compound **111** underwent a second Suzuki-coupling. Its reaction partner was now the ate-complex formed from the cyclohexyl-substituted vinylboronic acid **112** and aqueous NaOH. According to Roush *et al.*,[55] β-alkyl-*gem*-dibromoolefins undergo Suzuki couplings site-selectively with their *E*–C–Br bond. In agreement with that, we isolated the desired *Z*-configured monobromoolefin **113** in 79% yield. It was converted by Br/Li exchange into an organolithium compound. The latter was quenched by dropwise addition to an excess of neat ethyl chloroformate. This provided ethyl ester **114**. Upon exposure to HCl, the acetonide ring was cleaved and



Scheme 24[46] *Reagents*: i, Bu^tMe_2SiOTf (0.5 equiv.), CH_2Cl_2, 93% of the mixture; ii, DBU, $CHCl_3$; HCl, 96%.



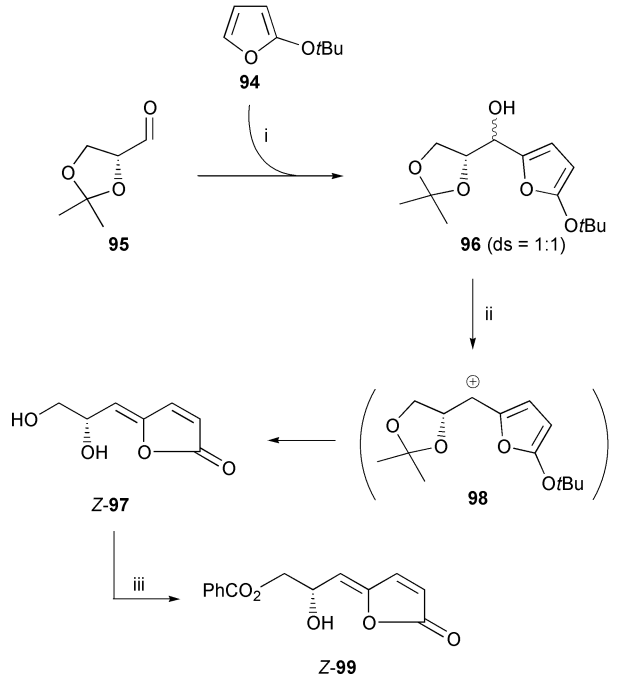
Scheme 25[47] *Reagents*: i, $BF_3{\cdot}OEt_2$–**90**–**81** 1 : 1 : 1, CH_2Cl_2, 56% (*lk*-**91** : *ul*-**91** > 99 : 1); ii, $ZnBr_2$–**90**–**81** 1 : 1 : 1, CH_2Cl_2, 61% (*ul*-**91** : *lk*-**91** = 87 : 13); iii, 3-ethynylfuran, $Pd(PPh_3)_4$, CuI, THF, iPr_2NEt, 70%; iv, same as (iii), 76%; v, diethyl azodicarboxylate, PPh_3, THF, 94% (*Z*-**93** : *E*-**93** = 92 : 8); vi, same as (v), 87% (*E*-**93** : *Z*-**93** = 98 : 2).

a spontaneous lactonization provided the γ-(α-hydroxyalkyl)-butenolide **115**. Its *anti*-selective dehydration was effected by treatment with excess PPh_3 and diethyl azodicarboxylate, *i.e.* by the established protocol of the dehydrations *lk*-**92** → free-lyngine (*Z*-**93**; Scheme 25) and *lk*-**84** → pandamarilactam-3y (*Z*-**85**, Scheme 23). In this way, we obtained butenolide **116** in 94% yield as a 95 : 5 *Z* : *E* mixture or, after recrystallization, in 90% yield as a pure isomer.

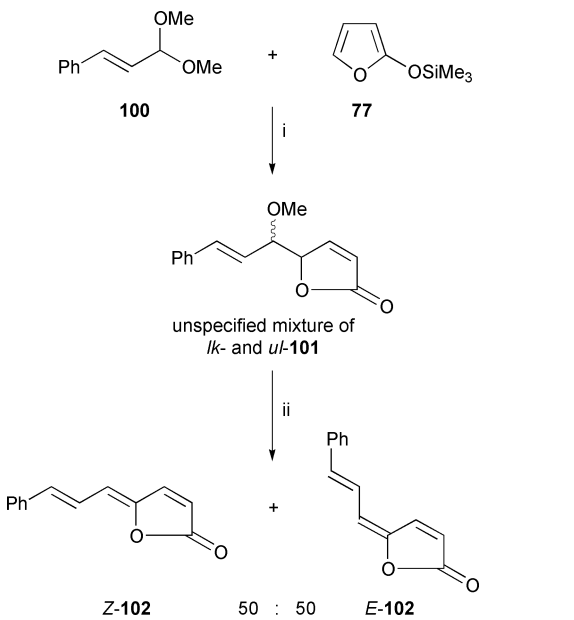
Other accesses to γ-alkylidenebutenolides

The best alternative to making *Z*-configured γ-alkylidenebutenolides by the β-elimination route of Scheme 1 is the metallocyclization/protonolysis strategy of Scheme 31. It has been pushed forward in recent years by the combined efforts of the Negishi, Rossi, and other groups.[31,32,35,38,49,50,56]

A reliable route to the less stable alkylidenebutenolides *E*-**119**, except the β-elimination route described, has yet to be developed. It seems conceivable, though, that the strategy of Scheme 32 could work. It represents a tandem metallocyclization/C,C-coupling approach and would start from pentenynoic acids **120** and unsaturated halides or triflates. While itself



Scheme 26[51] *Reagents*: i, Bu^{t}Li, **94**, THF, addition of **95**, 69%; ii, $TsOH{\cdot}H_2O$, THF, H_2O, 74%; iii, PhC(=O)CN, NEt_3, THF, 54%.



Scheme 27[52] *Reagents*: i, $TiCl_4$; ii, KOAc, HOAc, 80% over the two steps.

apparently unexplored, an analogous formation of *E*-configured γ-alkylidenebutanolides from pentynoic acids and aryl,[57] alkenyl,[58] or alkynyl halides (triflates) has been described.[59]

Notes and references

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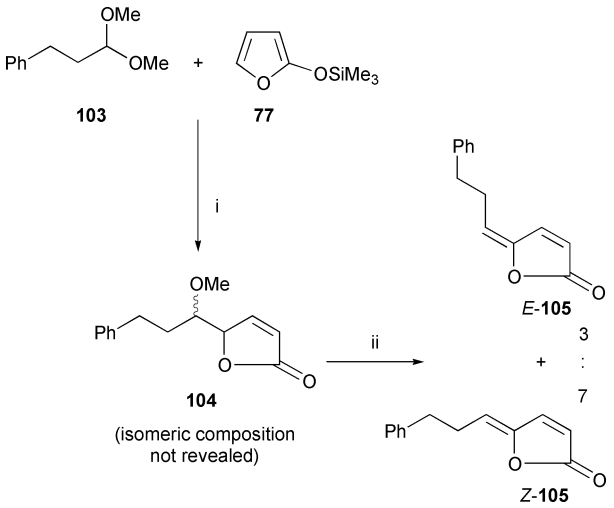
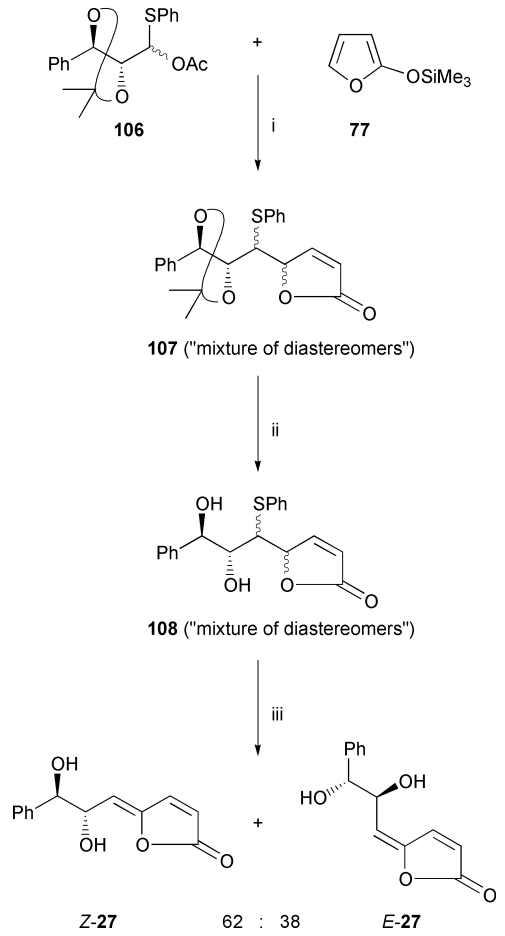
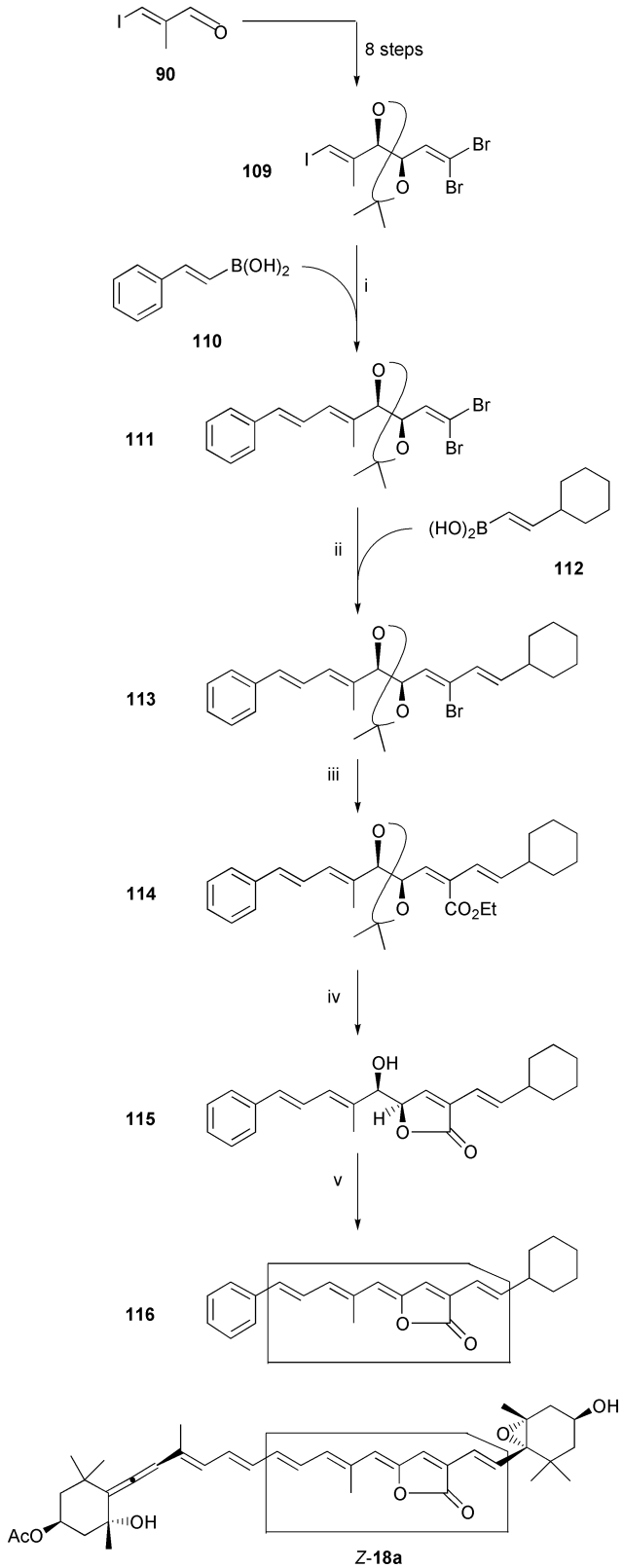


Scheme 28[43] *Reagents*: i, **103**:**77** 1:1.2, $SnCl_4$, CH_2Cl_2; aqueous HCl, 92%; ii, NaOAc, HOAc, 80%.



Scheme 29[53] *Reagents*: i, $SnCl_4$, CH_2Cl_2, 39–52% **107** (+ 7–15% **108** + 4% **27** as a *Z*,*E* mixture); ii, $F_3C–CO_2H$, H_2O, 84%; iii, AgF, pyridine, 68%.



Scheme 30[54] *Reagents and conditions*: i, $Pd(PPh_3)_4$, benzene, **116**; addition of **117**, aqueous NaOH, 56%; ii, $Pd(PPh_3)_4$, toluene, **118**; addition of **119**, aqueous NaOH, 79%; iii, Bu^tLi, Et_2O; addition to pure $ClCO_2Et$, 70%; iv, aqueous HCl, MeOH, 71%; v, PPh_3, THF; addition of diethyl azodicarboxylate, 90% after separation from 4% of the *E*-isomer.

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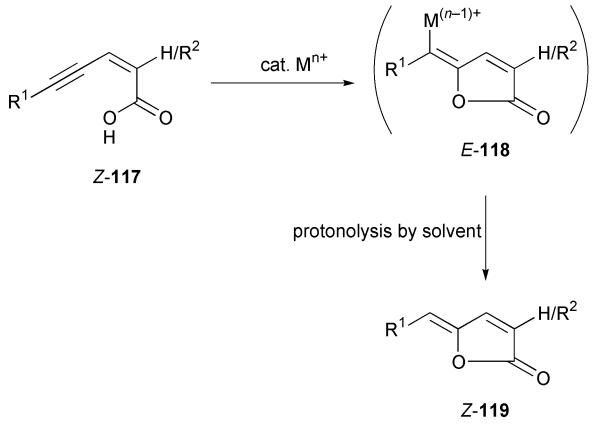
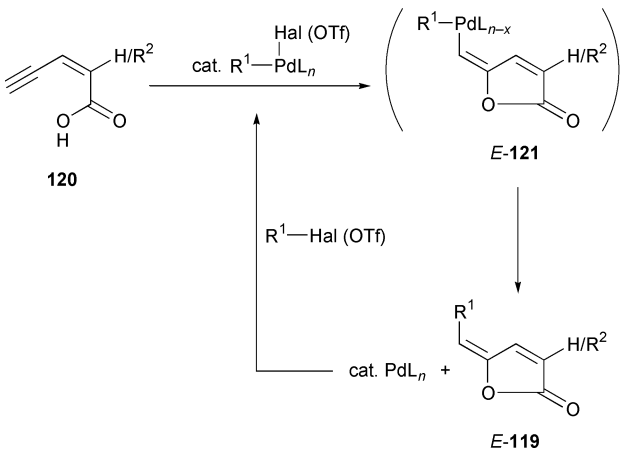


Scheme 31 *Z*-Selective generation of γ-alkylidenebutenolides by the metalolactonization of enynecarboxylic acids followed by protonolysis of the metalolactone.



Scheme 32 Suggested *E*-selective generation of γ-alkylidenebutenolides by the metalolactonization of pentenynoic acids followed by reductive elimination.

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