Natural Product Synthesis

Novel Strategy for the Synthesis of the Butenolide Moiety of Peridinin**

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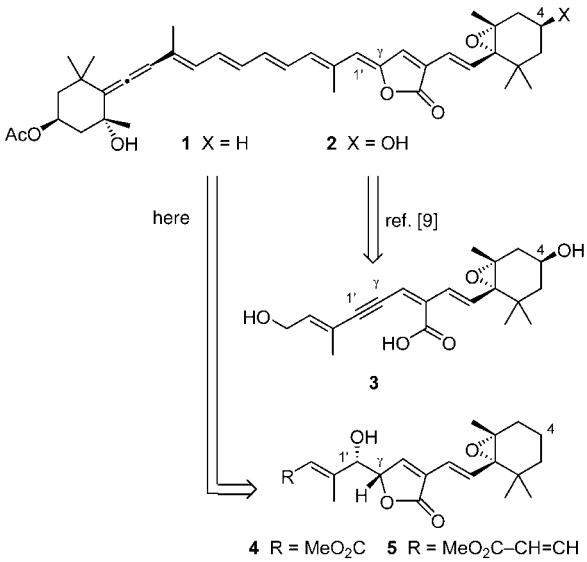
Peridinin (**2**,[1] Scheme 1) is one of the most common biosynthesized carotenoids on earth.[2] Its polyene chain contains an α-alkenyl-γ-alkylidenebutenolide unit, which



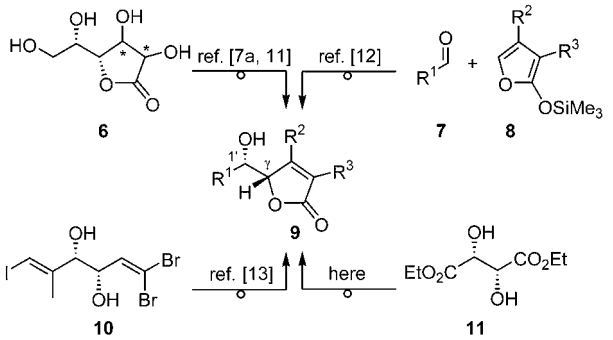
Scheme 1. Strategies for the syntheses of the butenolide moieties of peridinin (**2**) and deoxyperidinin (**1**).

has a *Z* configuration at the $C^{1'}=C^{\gamma}$ bond, as is typical for naturally occurring γ-alkylidenebutenolides.[3] Peridinin (**2**) plays a key role in marine photosynthesis[4] and displays considerable antitumor activity.[5] The fact that these roles are assumed solely by peridinin (**2**) and not by related carotenoids *may* be due or *supposedly*[5] is due to its butenolide ring, which, among carotenoids, is almost unique to **2**.[6]

As part of our study of the light-harvesting and cancerostatic properties of peridinin (**2**) and analogues such as deoxyperidinin (**1**, Scheme 1), we have developed a novel approach towards their α-alkenyl-γ-alkylidenebutenolide cores. In this communication we demonstrate this approach with the stereoselective syntheses of compounds **36** and **37** (Scheme 5), in which the last step is the *anti*-selective dehydration of the α-alkenyl-γ-(α-hydroxyalkyl)butenolides **4** and **5**, respectively (Scheme 1). We have employed dehydrations of this type en route to a number of stereodefined γ-alkylidenebutenolides.[7,8]

It should be possible to convert compounds **4**, **5**, **36**, and **37** into deoxyperidinin (**1**) by modification of the respective ester group. Likewise, appropriately hydroxylated analogues of compounds **4**, **5**, **36**, and **37** would be appropriate precursors for synthesizing peridinin (**2**). Two laboratory syntheses of **2** have been achieved so far. One was based on the stereocontrolled cyclization of enynoic acid **3** (Katsumura et al.[9]), the other used older, sophisticated, but stereorandom methodology (Ito et al.[10]).

Prior to the present study, we had established three different routes to diastereomerically pure γ-(α-hydroxyalkyl)butenolides **9**, which, through *anti* elimination, furnished pure *Z*-configurated γ-(alkylidene)butenolides (Scheme 2). These route were based on: modification of sugar lactones **6**;[7a,11] vinylogous Mukaiyama aldol additions of siloxyfurans **8** and aldehydes **7**;[12] and sequential C–Hal→C–C conversions of trihalodienediol **10**.[13] Here, in a fourth approach we started from (−)-diethyl tartrate (**11**; Scheme 2).



Scheme 2. Routes to γ-(α-hydroxyalkyl)butenolides **9**, which correspond to structures of type **4**/**5** in Scheme 1 and are precursors of γ-alkylidenebutenolides of type **1**/**2** structures in Scheme 1.

After acetalization of **11** (→**12**,[14] Scheme 3), formation of the double Weinreb amide furnished **13**; the yield (99%) was better than that of the published procedure (77%),[15] provided that the temperature was kept below −15°C throughout reaction and workup. Bis(amide) **13** thereby became available on the 40-g scale. Treatment of **13** with 1.0 equiv of MeMgBr gave rise to the monoketone **14** (66%).[16] Wittig olefination of this compound with ylides **15**[17] and **16**[18] delivered the unsaturated esters **17**[19]—as an 86:14 mixture of *E* and *Z* isomers[20] (pure *E* isomer was obtained in 77% yield from 10-g batches after separation by flash chromatography on silica gel[21])—and **18** (90% yield, which was isomerically pure with a *trans*,*E* configuration),[22] respectively. Compounds **17** and **18** both contain C(=O)-NMe(OMe) and C(=O)OMe units but reacted exclusively at the former upon treatment with $NaBH_4$ (optimally 8 equiv) in methanol. To the best of our knowledge, these are the first

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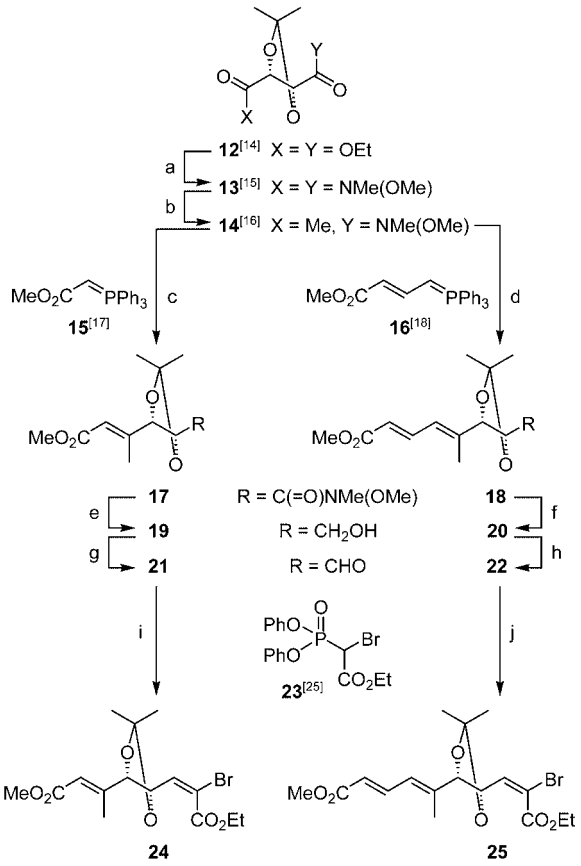
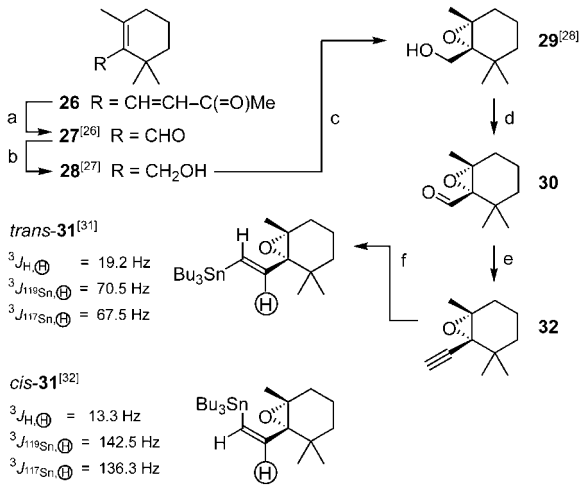


Scheme 3. Syntheses of bromoacrylate intermediates **24** and **25**. a) HNMe(OMe)·HCl (4 equiv), Me_3Al (4 equiv), CH_2Cl_2, −15 °C, 1 h, 99%; b) MeMgBr (1.0 equiv), THF, 0 °C, 1 h, 66%; c) **15** (2.0 equiv), toluene, reflux, 27 h, 77%, *E*:*Z* = 86:14; d) **16** (2.0 equiv), toluene, reflux, 30 h, 90%, *E*:*Z* > 99:1; e) $NaBH_4$ (8.0 equiv), MeOH, 25 °C, 18 h, 98%; f) same as (e) but 20 h, 92%; g) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), NEt_3 (6.0 equiv), −78 °C → 0 °C, 30 min, 90%; h) same as (g) but −78 °C, 90 min, 79%; i) **23** (1.2 equiv), NaH (1.0 equiv), THF, 0 °C, 30 min, 75%, *E*:*Z* = 95:5; j) same as (i) but 90 min, 82%, *E*:*Z* = 98:2. DMSO = dimethyl sulfoxide.

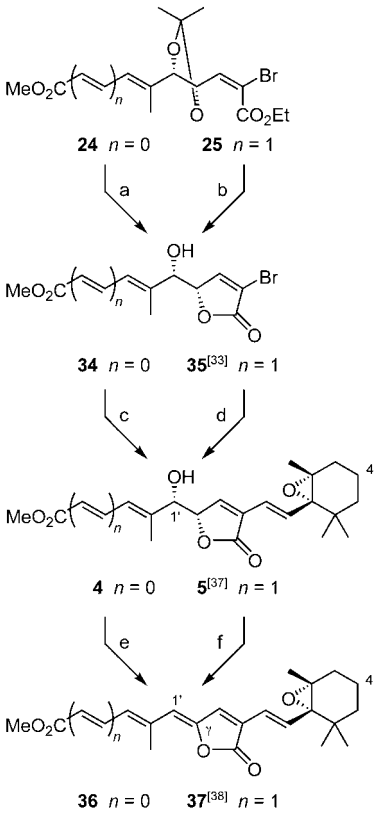


Scheme 4. a) O_3, MeOH, −78 °C, 2.5 h; Zn (1.5 equiv), HOAc/H_2O (1:1), 93%; b) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 1 h, 25 °C, 12 h, 76%; c) *t*BuOOH (2.0 equiv), $Ti(OiPr)_4$ (0.1 equiv), (−)-DIPT (0.1 equiv), 4 Å MS, CH_2Cl_2, −25 °C, 12 h, 67%, 99.8% *ee*; d) DMSO (3.0 equiv), $(COCl)_2$ (1.5 equiv), NEt_3 (4.5 equiv), −78 °C, 1 h, 99%; e) Bu_3SnH (1.1 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), THF, 25 °C, 2 h, 83%; f) $Me_3SiCH{=}N_2$ (1.2 equiv), LDA (1.2 equiv), −78 °C, 30 min, 57%. DIPT = diisopropyl tartrate, LDA = lithium diisopropylamide.

reductions of Weinreb amides effected with this reagent. The resulting hydroxy esters—**19** (98% yield) and **20** (92% yield)—were oxidized under Swern conditions[23] to afford the corresponding aldehyde esters (**21**, 90%; **22**, 79%). These were carried on to the α-bromoacrylates **24** (75%) and **25** (82%) with *E* stereoselectivities of 95:5 and 98:2, respectively, by using the Ando-type[24] bromophosphonate **23**,[25] which we developed to this end.

The preparation of the epoxycyclohexyl moiety of targets **4** and **5** started from β-ionone (**26**), which underwent ozonolysis and workup with Zn/HOAc to provide cyclocitral (**27**) in 93% yield (Scheme 4).[26] Subsequent reduction with $NaBH_4$ led to cyclogeraniol (**28**) in 76% yield.[27] This two-step procedure was two times more efficient than the one-step version in which the ozonolysis mixture was treated directly with $NaBH_4$ (→**28** in 30% yield). Asymmetric Sharpless epoxidation of **28** furnished the epoxy alcohol **29** in 67% yield.[28a,b] The *ee* value of **29** was 99.8% according to GC analysis of the trimethylsilyl ether. This surpasses the previously determined enantiopurities of **29**, regardless of whether it was synthesized in the same way (ref. [28a]: 95% *ee*; ref. [28b]: ≥98% *ee*) or by a different approach (ref. [28c]: 97.1% *ee*). Swern oxidation[23] delivered aldehyde **30** (99%). Because of the tendency of **30** to decompose, it was immediately C_1-extended with Shioiri's lithiodiazomethane[29] affording, after flash chromatography,[21] the volatile epoxyalkyne **32** in 57% yield. Pd-catalyzed hydrostannylation[30] gave the desired alkenylstannane *trans*-**31**[31] regio- and stereoselectively. The *trans* configuration of its C=C bond was deduced by comparison of the *H*–C=C–*H* and *Sn*–C=C–*H* coupling constants with those in the *cis* isomer.[32] For the *trans* isomer the first coupling constant is larger, for the *cis* isomer the second is larger (Scheme 4).

Scheme 5 shows the concluding steps of our syntheses. The next reaction was acetal cleavage of the bromodiester acetonides **24** and **25** mediated by Amberlyst 15 or preferably TsOH, which was followed by spontaneous formation of the butenolide rather than pentenolide unit. The resulting brominated γ-(α-hydroxyalkyl)butenolides **34** and **35**[33] were obtained in nearly quantitative yields. The ensuing step, a Stille coupling[34] with alkenylstannane *trans*-**31**, was catalyzed by bis(trifurylphosphane)palladium (generated in situ)[35] and cocatalyzed by CuI.[36] The final step was the *anti*-selective dehydration to form the *Z*-configurated $C^{1'}{=}C^{\gamma}$ bond. It was realized under Mitsunobu conditions, i.e., by treatment of γ-(α-hydroxyalkyl)butenolides **4** and **5**[37] with 2 equiv of both of PPh_3 and DEAD, at −30 °C. These conditions were gleaned from earlier experience in our group.[12,13] While γ-alkylidenebutenolide **36** was obtained in isomerically pure form from reaction in anhydrous THF followed by aqueous workup and standard flash chromatography on silica gel,[21] the vinologous γ-alkylidenebutenolide



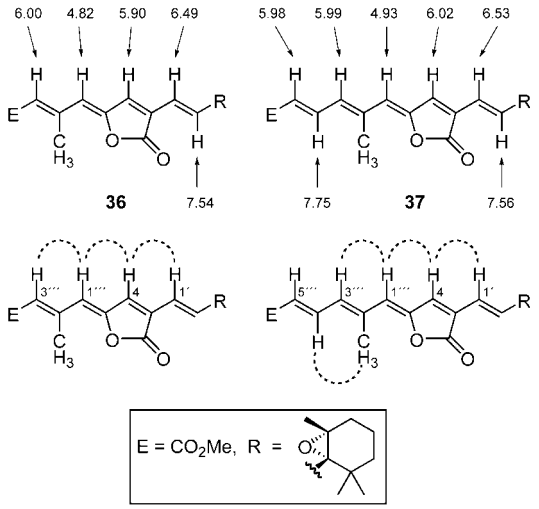
Scheme 5. Butenolide syntheses. a) MeOH, Amberlyst 15, reflux, 28 h, 95%; b) MeOH, TsOH (0.05 equiv), reflux, 1 h, 94%; c) *trans*-**31** (1.2 equiv), CuI (1.65 equiv), $[Pd_2dba_3]\cdot CHCl_3$ (0.05 equiv), P(2-furyl)$_3$ (0.3 equiv), NMP, 25 °C, 19 h, 84%; d) same as (c), 82%; e) DEAD (2.0 equiv), PPh_3 (2.0 equiv), THF, −30 °C, 90 min, 62%; f) same as (e) except for THF (degassed, 250 ppm di-*tert*-butylcresol) and exclusion of light, 90%. DEAD = diethyl azodicarboxylate, NMP = *N*-methylpyrrolidone, Ts = *para*-toluenesulfonyl.

37 was just one constituent of a mixture of the four 1,3-diene isomers. Compound **37**[38] could be prepared free from isomers only when:

- daylight was excluded throughout the reaction and chromatography,
- the solvent (THF) was degassed and contained di-*tert*-butylcresol as a radical scavenger,
- no aqueous workup was performed but rather the solvent was removed by vacuum distillation at −30 °C,
- and the cyclohexane/ethyl acetate mixture used as the eluent in flash chromatography was degassed. Remarkably, the yield of **37** was then 90%.[39]

The configurational assignments of the double bonds in our target structures **36** and **37** were based on the magnitudes of the olefinic $^3J_{H,H}$ couplings (for the configurations of the disubstituted C=C bonds) and on the NOEs indicated in Scheme 6 (for the configurations of the trisubstituted C=C bonds).

In summary, the present study establishes that diethyl tartrate is a viable precursor of stereopure *Z*-γ-alkylidenebutenolides. Moreover, extensions of this approach should make



Scheme 6. ^{1}H NMR experiments (500 MHz): NOEs (– – –; **36** in $CDCl_3$ and **37** in C_6D_6); characteristic chemical shifts for alkylidenebutenolides **36** and **37** (both in C_6D_6).

both deoxyperidinin (**1**) and peridinin (**2**) accessible by total synthesis.

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[20] The reaction of monoketone **14** and the sodium derivative of $(EtO)_2P(=O)-CH_2-CO_2Et$ gave the ethyl ester/Weinreb amide analogue of **17** as an *E*:*Z* mixture (93% yield, *E*:*Z* = 59:41).

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[37] (5*S*)-3-{(*E*)-2-[(1*S*,2*R*)-1,2-Epoxy-2,6,6-trimethylcyclohexyl]-ethenyl}-5-[(2*E*,4*trans*,1*S*)-1-hydroxy-5-(methoxycarbonyl)-2-methyl-2,4-pentadienyl]-2(5*H*)-furanone (**5**): ^{1}H NMR (500.0 MHz, $CDCl_3$): $\delta = 0.93$, 1.13 and 1.15 [3 × s, 2″-CH_3, 6″-$(CH_3)_2$], 1.06–1.10 (m, 5″-H^1), ca. 1.39–1.49 (m, 4″-H^1, 5″-H^2), 1.61–1.68 (m, 4″-H^2), AB signal ($\delta_A = 1.75$, $\delta_B = 1.90$, $^{2}J_{AB} = 15.1$ Hz, additionally split by $J_{A,4''\text{-H}(1)} = J_{A,4''\text{-H}(2)} = 5.2$ Hz, $J_{B,4''\text{-H}(1)} = J_{B,4''\text{-H}(2)} = 7.6$ Hz, 3″-H_2), 1.99 (d, $^{4}J_{2'''\text{-Me},3'''} = 1.4$ Hz, 2‴-CH_3), 2.57 (br s, OH), 3.77 (s, OCH_3), 4.18 (d, $J_{1''',5} = 6.2$ Hz, 1‴-H), 5.01 (m_c, approximately interpretable as dd, $J_{5,1'''} = 6.3$ Hz, $J_{5,4} = 1.9$ Hz, 5-H), 5.95 (d, $J_{5''',4'''} = 15.3$ Hz, 5‴-H), 6.28 (m_c, approximately interpretable as ddq, $J_{3''',4'''} = 11.6$ Hz, $^{4}J_{3''',5'''} \approx 1.4$ Hz, $^{4}J_{3''',2'''\text{-Me}} \approx 0.8$ Hz, 3‴-H), 6.29 (d, $J_{1',2'} = 15.7$ Hz, 1′-H), 6.95 (d, $J_{4,5} = 2.1$ Hz, 4-H), 7.22 (d, $J_{2',1'} = 15.6$ Hz, 2′-H), 7.57 ppm (dd, $J_{4''',5'''} = 15.1$ Hz, $J_{4''',3'''} = 11.5$ Hz, 4‴-H).

[38] (5*Z*)-3-{(*E*)-2-[(1*S*,2*R*)-1,2-Epoxy-2,6,6-trimethylcyclohexyl]-ethenyl}-5-[(2*E*,4*trans*)-5-(methoxycarbonyl)-2-methyl-2,4-pentadienylidene]-2(5*H*)-furanone (**37**): To a solution of γ-(α-hydroxyalkyl)butenolide **5** (22.4 mg, 55.7 μmol) in THF (3 mL; the solvent contained 250 mg 2,6-di-*tert*-butyl-4-cresol per L and was degassed prior to use) was added DEAD (17.6 μL, 19.4 mg, 111 μmol, 2.0 equiv) at −30 °C under argon atmosphere and exclusion of light. After 10 min PPh_3 (29.2 mg, 111 μmol, 2.0 equiv) was added, and the reaction mixture was stirred at −30 °C for another 2 h. Two-thirds of the solvent was removed under reduced pressure at −30 °C. A small portion of chromatography eluent (1 mL) was added, and this mixture was subjected to flash chromatography (cyclohexane:EtOAc 10:1 with 0.7 vol% NEt_3; degassed) which rendered the product (19.2 mg, 90%) as an intensely yellow solid. For selected ^{1}H NMR (500.0 MHz, C_6D_6) data see Scheme 6.

[39] Following the suggestion of a referee, we also conducted the Stille coupling of the (dienoic ester)-containing bromobuteno-

lide **35** and the (4*S*)-4-hydroxy analogue of *trans*-**31**.[30] This provided the (4*S*)-4-hydroxy analogue of **5,** a precursor of the hydroxylated butenolide moiety of natural peridinin with unaltered yield (83%). Because of the presence of the 4-hydroxy group, which had to be conserved, the subsequent activation of the 1′-hydroxy group was best carried out under modified conditions: treatment of (4*S*)-4-hydroxy-**5** at −10°C in THF with 9 equiv each of DEAD and PPh_3 (71% yield). In the same way, when we processed the aldehyde analogue of the ester-substituted bromobutenolide **35**, we could swap the steps, i.e., start with the elimination and couple with the (4*S*)-4-hydroxy analogue of *trans*-**31**. The detailed results will be reported in a full paper.

