Olefin Synthesis

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Decarboxylative Grob-Type Fragmentations in the Synthesis of Trisubstituted *Z* Olefins: Application to Peloruside A, Discodermolide, and Epothilone D**

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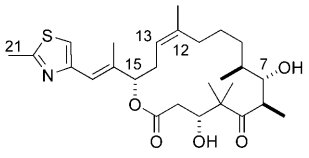
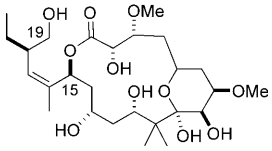
Dedicated to Professor Albert Eschenmoser

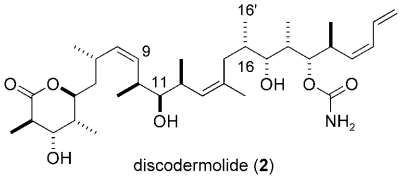
The stereocontrolled synthesis of methyl branched trisubstituted *Z* olefins has been pursued intensively during the past few years, as this structural motif is found in numerous polyketides with promising anticancer activity, such as epothilone D (**1**), discodermolide (**2**), and peloruside A (**3**).



epothilone D (**1**)



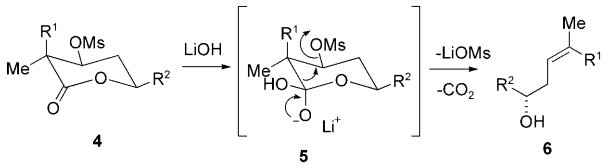
peloruside A (**3**)



discodermolide (**2**)

As a result of these extensive efforts, a variety of approaches have emerged based on carbonyl olefination, olefin metathesis, alkyne functionalization, allylic rearrangements, and cross-coupling reactions.[1] As most of these protocols make use of expensive and/or toxic reagents, we wondered why E2 elimination reactions, and in particular Grob fragmentations with their simple operability and virtually "green" conditions, have been neglected in the construction of acyclic olefins.[2] After all, Grob fragmentations have been rediscovered for the generation of cycloolefins.[3]

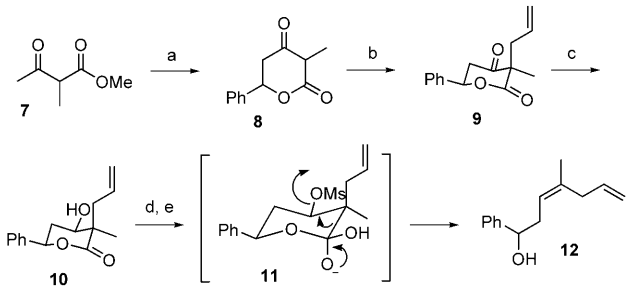
Herein we report a novel hydroxide-induced decarboxylative Grob-type fragmentation and its application to the synthesis of compounds **1**–**3**.[4] Our strategy was centered around mesyloxy lactones such as **4** (Scheme 1). The addition



Scheme 1. Grob-type hydroxide-induced fragmentation of lactone **4**. Ms = methanesulfonyl.

of a hydroxide ion leads to the tetrahedral intermediate **5**, which undergoes fragmentation to form olefin **6** stereounambiguously. In the preparation of lactone **4**, three stereogenic centers, one of which is quaternary, must be generated with the relative configurations indicated. For stereoelectronic reasons, clean fragmentation can be expected when the hydroxide ion attacks axially and the lactone adopts a chair conformation with the OMs substituent in an equatorial position.[5] This conformation may be facilitated by introducing a bulky residue R^2 *cis* to the OMs group.

To prove the feasibility of the approach a simplified racemic test system was developed (Scheme 2). Lactone **8** was



Scheme 2. Model study. a) LDA, HMPA, then PhCHO, THF, −78 °C; 1 M KOH, then HCl, 0 °C, 64% (2 steps); b) $[Pd(PPh_3)_4]$, allyl acetate, K_2CO_3, $BnEt_3NCl$, EtOAc/H_2O, 98%, d.r. 4:1; c) $NaBH_4$, MeOH, 0 °C, 97%. d) MsCl, Et_3N, Et_2O, −10 °C; e) KOH, MeOH, 0 °C, >95% (2 steps). Bn = benzyl, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide.

prepared, and the quaternary center was introduced by a biphasic Trost–Tsuji allylation.[6] After reduction of the β-carbonyl group, diastereomer **10** was mesylated to give **11**, which was treated with sodium hydroxide in methanol at 0 °C to give *Z* olefin **12** as the sole product in quantitative yield.

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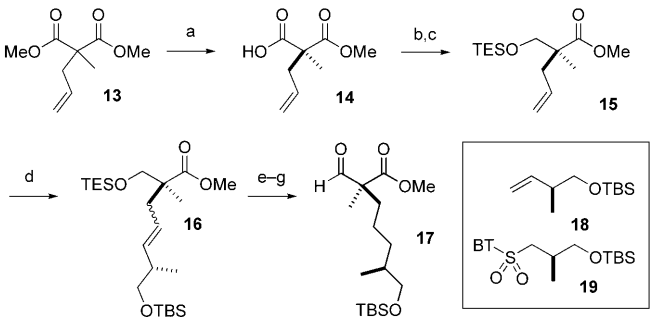
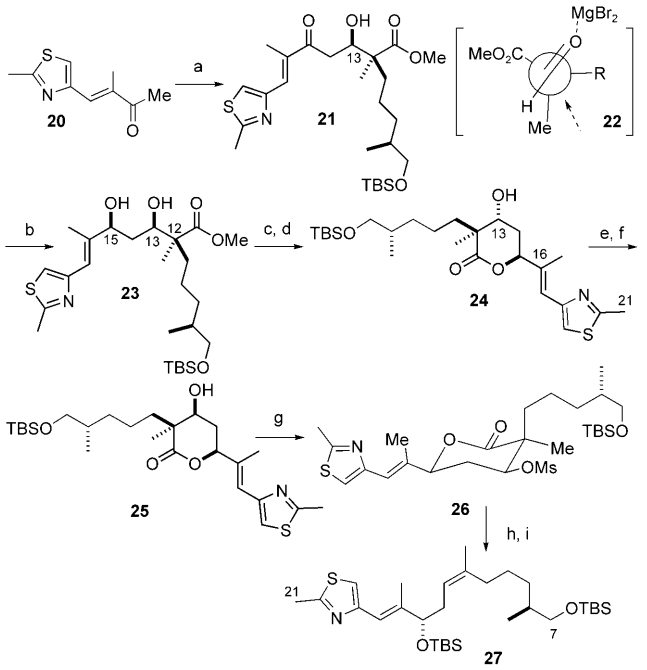
Encouraged by this result, we applied our method to the synthesis of **1** (Schemes 3 and 4). To obtain a compound with uniform chirality at C15, lactone **26** had to be prepared in a diastereo- and enantioselective manner. We started with the quaternary center,[7] which then served to control the formation of the remaining centers by means of a stereochemical relay. Hence, malonate **13** was hydrolyzed with pig liver esterase (PLE) to provide the monocarboxylic acid **14** with 95% *ee*,[8] which was readily converted into silyl ether **15**, a general building block whose allylic appendage can be modified in many ways. Thus, for the synthesis of **1**, chain elongation of **15** to give **16** was accomplished in high yields either by cross-metathesis with **18** or by modified Julia olefination with **19**.[9,10] From **16**, aldehyde **17** was available in three simple steps with 83% overall yield.



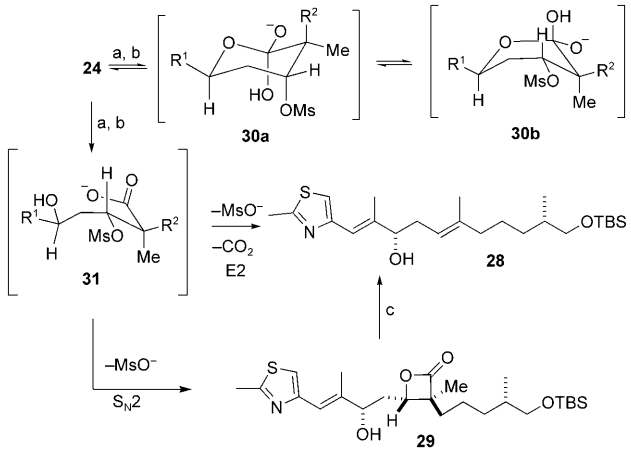
Scheme 3. Conversion of malonate **14** into aldehyde **17**. a) PLE, 0.05 M KH_2PO_4, 90%; b) ClC(O)OMe, Et_3N, THF, 0°C; $NaBH_4$, MeOH, 0°C, 75%; c) TESCl, py, RT, quant; d) Grubbs–Hoveyda cat., **18**, CH_2Cl_2, reflux, 93% or 1. O_3, PPh_3, PPTS, CH_2Cl_2, −78°C, quant.; 2. LiHMDS, **19**, THF, −78°C to −30°C, 96%; e) PPTS, MeOH, RT, 92%; f) PtO_2, H_2, EtOAc, 99%; g) DMP, CH_2Cl_2, 0°C, 91%. BT = 2-benzothiazolyl, DMP = Dess–Martin periodinane, HMDS = hexamethyldisilazane, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

Next, aldehyde **17** was activated with freshly prepared $MgBr_2{\cdot}Et_2O$ and then added to the lithium enolate of ketone **20**. Adduct **21** was obtained as single 13*R* diastereomer in 91% yield, presumably via the Felkin–Anh transition state **22**. Even with stronger Lewis acids, a chelated transition state could not be induced. Substrate-controlled *syn* reduction with catecholborane yielded the dihydroxy ester **23**, whose saponification and lactonization led to lactone **24**.[11] Clean inversion at C13 was achieved by means of an oxidation–reduction sequence to give **25**. Subsequent mesylation and fragmentation delivered the C7–C21 fragment **27** of epothilone D (16 steps, 27% overall yield). Compound **25** was identical in every respect with an authentic sample,[12b] which served as an intermediate in several approaches to **1**.[12a–c]

To extend the scope of the fragmentation protocol, we investigated lactone **24** (Scheme 5). Because of the axial configuration of the 13-OH group,[13] a Grob-type fragmentation in a chair conformation should not be possible. On the other hand, the boat conformation **30b** might be suitable stereoelectronically to undergo fragmentation although the species is energetically unfavorable. Nevertheless, olefin **28** (38% yield) was obtained under the usual conditions, along with β-lactone **29** (52% yield). This result may be rationalized in terms of a ring opening of **24** to form carboxylate **31**, which undergoes both fragmentation to give *E* olefin **28** and S_N2 cyclization to form the β-lactone **29**.[14] Thermolysis of **29** also gave **28**, so that, overall, olefin **28** is obtained in *E* geometry exclusively and acceptable yield. This result underlines the versatility of the method, as both the *Z* and the *E* olefins are available from lactone **24** by analogous routes.

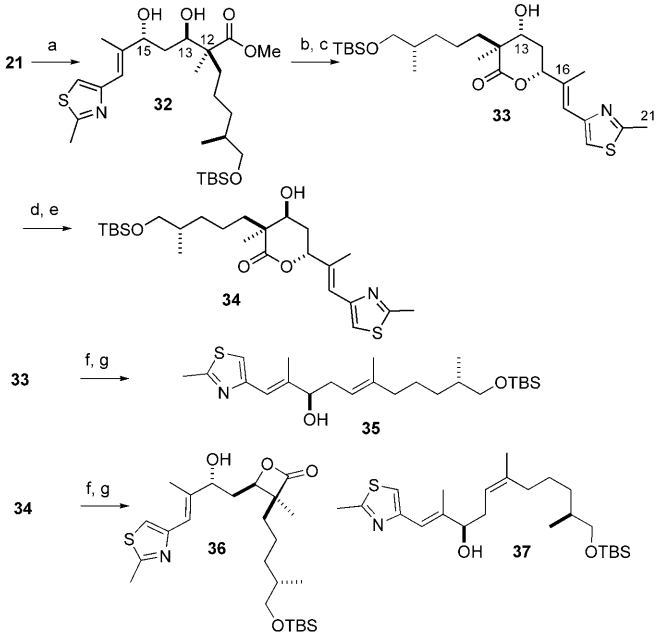


Scheme 4. Synthesis of the C7–C21 fragment **27** of epothilone D. a) LiHMDS, THF, −78°C, then **17**, $MgBr_2{\cdot}Et_2O$, 91%; b) catecholborane, THF, −10°C, 88%; c) LiOH, THF, 0°C; d) EDC·HCl, DMAP, CH_2Cl_2, 94% (2 steps); e) DMP, $NaHCO_3$, CH_2Cl_2, 94%; f) $NaBH_4$, MeOH, −78°C, 93%; g) MsCl, Et_3N, Et_2O, 0°C; h) LiOH, THF, 0°C, 81%; i) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, quant. DMAP = 4-(dimethylamino)pyridine, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, OTf = trifluoromethanesulfonate.



Scheme 5. Fragmentation of lactone **24**. a) MsCl, Et_3N, Et_2O, 0°C; b) LiOH, THF, 0°C, 38% (**28**) and 52% (**29**); c) DMF, reflux, 85%.

An additional degree of freedom lies in the configuration of center C15 (Scheme 6). Thus, after the reduction of ketone **21** to *anti*-diol **32**, lactones **33** and **34** were available.[15] Fragmentation of **33** via the chair transition state cleanly led



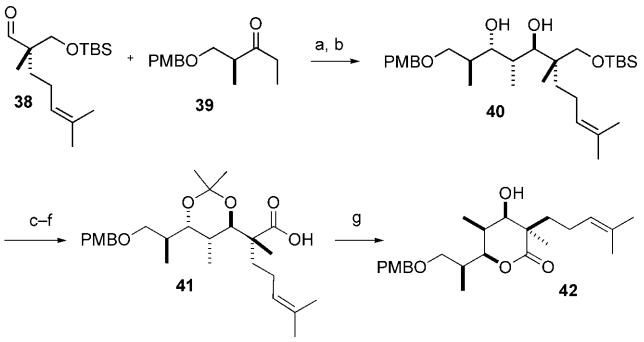
Scheme 6. Fragmentation of lactones **33** and **34**. a) $Me_4NBH(OAc)_3$, CH_3CN/AcOH, −30 °C, 87%; b) LiOH, THF, 0 °C; c) EDC·HCl, DMAP, CH_2Cl_2, 85% (2 steps); d) DMP, $NaHCO_3$, CH_2Cl_2, 94%; e) $NaBH_4$, MeOH, −78 °C, 90%; f) MsCl, Et_3N, Et_2O, 0 °C; g) LiOH, THF, 0 °C, 64% (**35**), 36% (**36**), 52% (**37**).

to the *E* olefin **35**, whereas **34** gave β-lactone **36** and the *Z* olefin **37**, presumably via the carboxylate. Thus, four diastereomers of the northern fragment of **1** are available from intermediate **21** using the same fragmentation approach.

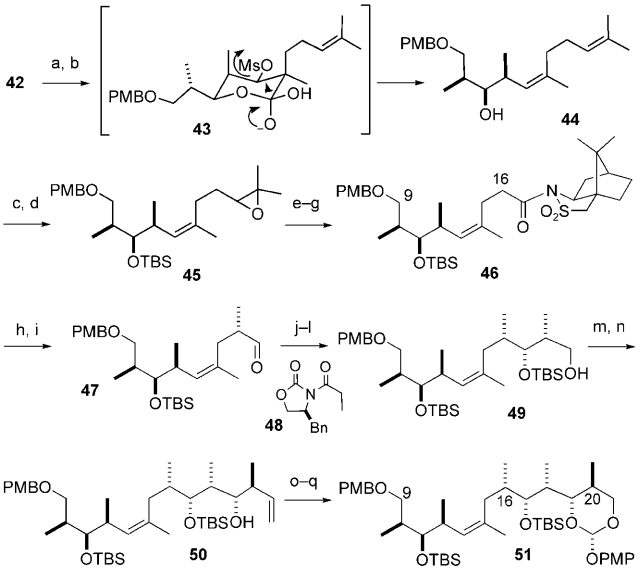
For approaching **2**, the required quaternary center was introduced via known aldehyde **40** (Scheme 7).[16] An *anti*-selective aldol addition with ketone **41** was used to construct lactone **44** stereoselectively.[17] To intersect Smith's C9–C21 discodermolide intermediate **51** (Scheme 8),[18] lactone **42** was fragmented to the *Z* olefin **44** and then transformed into the Oppolzer sultam **46**.[19] Asymmetric methylation followed by reduction gave aldehyde **47**, which was used in a *syn*-selective Evans aldol addition. The remaining two stereocenters were installed by a Roush crotylation.[20] Oxidative cleavage of the terminal olefin, via the epoxide, led to the free 19,21-diol, which was protected as the PMP acetal **51**, whose analytical data were in full agreement with those reported.[18]

For the synthesis of the peloruside A fragment **58** (Scheme 9), enantiomerically pure monocarboxylic acid **52** was converted to aldehyde **53**.[21] Evans aldolization with oxazolidinone **54** gave lactone **55**,[22] whose fragmentation led to the *Z* olefin **57** stereoselectively. For further manipulation, the protecting groups were changed to give fragment **58**.[23]

In conclusion we have shown that decarboxylative Grob fragmentations are a versatile tool for the stereoselective construction of chiral trisubstituted *Z* olefins. In contrast to

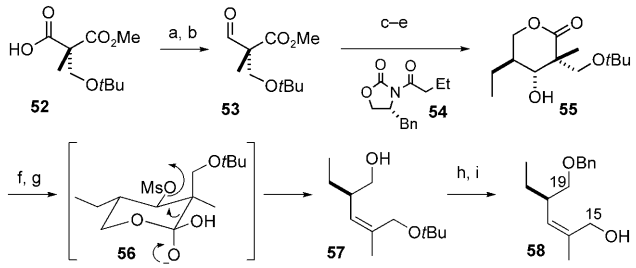


Scheme 7. Synthesis of **47**, the precursor for the fragmentation to give discodermolide. a) Cy_2BCl,Et_3N, **39**, then **38**, Et_2O, −78 °C to 0 °C, 76%; b) $Me_4NBH(OAc)_3$, CH_3CN/AcOH, −30 °C, 94% (b.r.s.m.); c) dimethoxypropane, CSA, CH_2Cl_2, RT, 86%; d) 35% HF·py, CH_3CN, RT, 97%; e) IBX, EtOAc, reflux, 86%; f) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, *tert*-butyl alcohol/H_2O, RT, quant.; g) CSA, CH_2Cl_2, RT, 83%. b.r.s.m. = based on recovered starting material, CSA = camphorsulfonic acid, Cy = cyclohexyl, IBX = 2-iodoxybenzoic acid, PMB = *para*-methoxybenzyl.



Scheme 8. Conversion to fragment **51** of discodermolide. a) MsCl, DMAP, py, CH_2Cl_2, RT; b) LiOH, THF, RT, 88% (2 steps); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, quant.; d) *m*CPBA, NaOAc, CH_2Cl_2, −20 °C, 92%; e) $HIO_4·2H_2O$, THF/Et_2O, 0 °C, 90%; f) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, *tert*-butyl alcohol/H_2O, RT, quant.; g) (1*R*)-camphor-2,10-sultam, DIC, DMAP, CH_2Cl_2, RT, 96%; h) NaHMDS, MeI, THF, −78 °C, 89%; i) DIBAL-H, CH_2Cl_2, −100 °C, 94%; j) Bu_2BOTf, Et_3N, **48**, then **47**, CH_2Cl_2, −78 °C to 0 °C, 65% (99% b.r.s.m.); k) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, quant.; l) $LiBH_4$, Et_2O, MeOH, 0 °C, 86%; m) IBX, DMSO, RT; n) (*R*,*R*)-diisopropyl tartrate (*E*)-crotylboronate, toluene, −78→0 °C, 87%; o) $[VO(acac)_2]$, *t*BuOOH, CH_2Cl_2, 0 °C, 87% (2 steps); p) $HIO_4·2H_2O$, Et_2O/THF, 0 °C, 51% b.r.s.m.; q) anisaldehyde dimethyl acetal, CSA, CH_2Cl_2, RT, 86%. acac = acetylacetonate, DIBAL-H = diisobutylaluminum hydride, DIC = *N*,*N*′-diisopropylcarbodiimide, *m*CPBA = *m*-chloroperbenzoic acid, PMP = *p*-methoxyphenyl.

conventional syntheses of such systems, which put the olefination step at the end of the sequence, we start with the formation of the olefin moiety from chiral aldehydes such as **17**, **38**, and **53**, and use their stereogenic information for the



Scheme 9. Synthesis of the C15–C19 fragment of peloruside A. a) ClC(O)OMe, Et_3N, THF, 0°C; $NaBH_4$, MeOH, 0°C, 83%; b) IBX, DMSO, RT, 80%; c) Bu_2BOTf, Et_3N, **56**, then **55**, CH_2Cl_2, −78→0°C, 85%; d) $LiBH_4$, Et_2O, MeOH, 0°C, 80%; e) K_2CO_3, MeOH, RT, 1 N HCl, quant.; f) MsCl, DMAP, CH_2Cl_2, RT, 99%; g) LiOH, dioxane, RT, 83%; h) BnBr, Ag_2O, TBAI, quant.; i) TFA, CH_2Cl_2, RT, 91%. TBAI = tetrabutylammonium iodide, TFA = trifluoroacetic acid.

construction of additional chiral centers on the chain. Further benefits of the approach lie in its high overall yield, high connectivity and compatibility with aldol reactions, high stereocontrol, mild conditions, and simple reagents. Most steps of the sequence are not time-consuming and the intermediates do not require purification. Studies on the scope and limitation as well as further applications to natural product synthesis are underway in our laboratory.

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