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The Total Synthesis of Epothilone D as a Yardstick for Probing New Methodologies

Alexander M. Haydl and Bernhard Breit*

Abstract: Herein, we report on a concise and highly convergent synthesis of epothilone D, relying on fragments of equal complexity which could be prepared in gram scale quantities. The strategy to construct the fragments comprises the use of our reported enantiospecific zinc-catalyzed cross-coupling of an *α*-hydroxy ester triflate with a Grignard reagent, the application of our hydroboration/boron-magnesium exchange sequence for the rapid construction of the *Z*-substituted trisubstituted double bond present in the natural product and on a Noyori-type hydrogenation to install the *β*-hydroxy ester moiety of the southern part. The key to success is our diastereoselective "head-to-tail" macrolactonization by an intramolecular addition of the corresponding *ω*-alkinyl-substituted carboxylic acids to construct a new stereocenter in the macrocyclic core structure in just a single step.

Polyketides prevail in a large variety of natural products and hold an up to five times higher chance to possess biological activity, compared to any other class of natural products.[1,2] Aside from a high level of molecular complexity, natural products holding macrocyclic lactones in particular exhibit a broad spectrum of biological activitiy,[3] such as antineurodegenerative,[4a,b] anticancer,[4c] antibiotic,[4d] olfactory,[4e] and various others.[4f]
Many different strategic approaches for the synthesis of macrocyclic core structures, besides the classical lactonization conditions by anhydride-type activation of the corresponding *ω*-seco-acids have been reported in the recent past,[5] including ring-closing metathesis,[6a,b] Diels-Alder macrocyclization,[6c] intramolecular cross-coupling reactions,[6d,e] metal-catalyzed coupling reactions,[6f-h] or Horner-Wadsworth-Emmons-type olefinations.[6i] However, the development of improved strategic approaches facing modern demands for resource efficiency in organic chemistry in order to construct macrolactones remains a highly active and challenging field of research. Our research group developed a rhodium catalyzed[7] atom-economical and regioselective addition of pronucleophiles to allenes and alkynes,[8] a method which could be seen as an alternative to metal-catalyzed allylic substitution[9] and oxidation[10] to generate branched allylic esters.[11] Particularly the hydrooxycarbonylation reaction using carboxylic acids[12,13] as suitable pronucleophiles, hence representing a C-O bond-forming addition reaction to form branched allylic esters emerged as a suitable concept to construct macrolactones. Emanating from *ω*-allenyl-substituted carboxylic acids, a broad range of enantiopure branched allylic

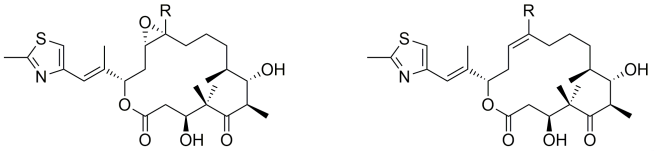
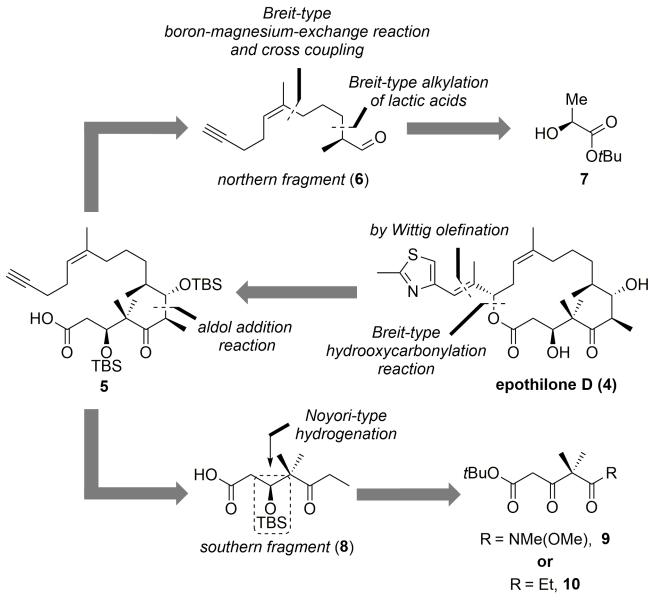


Figure 2. The polyketides epothilone A-D as representative examples of macrolactone-based and highly bioactive natural products.

macrolactones[14a] could be obtained and furthermore this approach proved successful in a number of total synthesis reported by us in the recent past.[15] The use of *ω*-alkinyl-substituted carboxylic acids also brought the same type of valuable macrocycles into reach, however to date only in a racemic fashion.[14b] Driven by our curiosity as to whether this initial methodology would allow therefore a diastereoselective approach of macrocycles just by substrate control in natural product syntheses, we targeted epothilone D (**4**, Figure 1).[16]
Due to its enhanced antiproliferative activity against several human cancer cell lines, the natural product family of the epothilones[17] has already garned significant attention from organic chemists in the recent past, although from a medicinical point of view their importance has waned.[18]
Given the 16-membered macrolactone core, epothilone D (**4**) was retrosynthetically dismantled as outlined in Scheme 1. Hence, we envisioned that an intramolecular diastereoselective hydrooxycarbonylation of the corresponding *ω*-alkinyl-substituted carboxylic acid **5** might provide straightforward



Scheme 1. Envisioned retrosynthetic disconnection of epothilone D.

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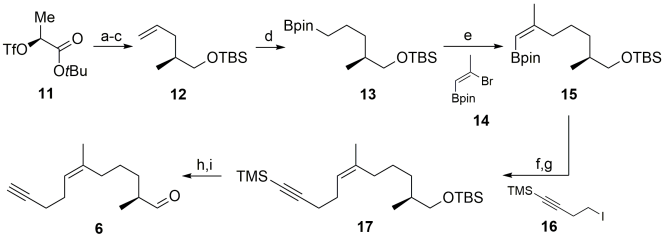
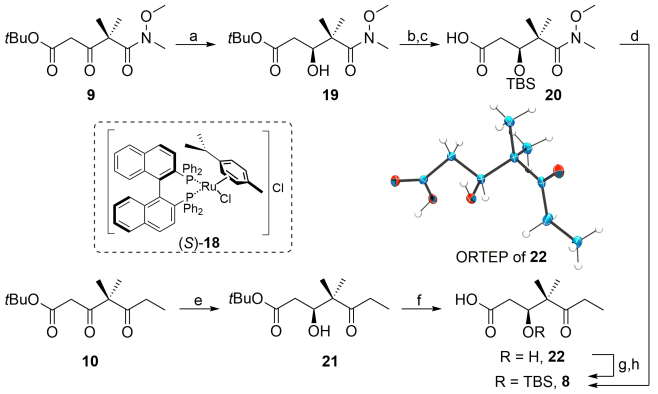


Scheme 2. Preparation of the northern fragment. Reagents and conditions: a) $ZnCl_2$ (10 mol%), allylmagnesium chloride, THF, -10 °C the 0 °C, 3 h, 68 %, 91 % *ee*; b) $LiAlH_4$. Et_2O, 0 °C, 2 h, 90 %; c) TBSCl, imidazole, 4-DMAP (10 mol%), CH_2Cl_2, room temperature, 24 h, 86 %; d) [{Rh(CO)$(PPh_3)_2$Cl}] (1.0 mol%), HBpin, THF, room temperature, 6 h, 93 %; e) 1,4-di(chloromagnesium)butane, $ZnBr_2$, [{$Pd(PPh_3)_2Cl_2$}] (5.0 mol%), **14**, toluene/THF, 0 °C then room temperature, 24 h, 91 %; f) aq. NaOH, I_2, THF, room temperature, 2.5 h, 97 %; g) **16**, *t*BuLi, $ZnBr_2$, [{$Pd(PPh_3)_2Cl_2$}] (5.0 mol%), THF, -78 °C then room temperature, 18 h, 90 %; h) TBAF, THF, 18 h, room temperature, 98 %; i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C then room temperature, 1 h, 94 %. Bpin=pinacolboronate, DMSO=dimethylsulfoxide, TBAF=tetra-*N*-butylammonium fluoride, TBS=*tert*-butyldimethylsilyl, Tf=trifluoromethanesulfonyl, TMS=trimethylsilyl.

access in order to obtain the core of **4**. At the same time, the interim structure should bring a valuable allylester moiety into reach, which could then be further elaborated to its parental compound epothilone D (**4**) by a subsequent Wacker-type oxidation, followed by a Wittig olefination to introduce the thiazole-based heterocycle and a final overall deprotection. Similar as in earlier total syntheses of epothilone B or D, our retrosynthetic approach could be traced back to the use of the literature known southern fragment **8** to be connected with the northern fragment **6** by an aldol addition reaction.[19] The synthetic plan for the synthesis of the southern fragment **8** involves a Noyori-type asymmetric hydrogenation of either 3-oxoglutaric acid derivative **9**[20a] or *β*,*γ*-diketoester **10**.[20b] Simultaneously, the construction of the northern fragment **6** relies on two methodologies reported earlier by our group. A reaction sequence emanating from commercially available *L*-(+)-lactic acid ester **7** and including the enantiospecific zinc-catalyzed cross-coupling of *α*-hydroxy ester triflates with Grignard reagents[21] and a subsequent hydroboration/boron-magnesium exchange sequence[22] for the rapid construction of the *Z*-substituted trisubstituted double bond was envisioned in this respect.

The synthesis of the northern fragment **6** commenced by starting from the enantiopure literature known triflate **11** (>99 % *ee*),[21,23] itself derived from (-)-*tert*-butyl *L*-lactate and directly subjected to our earlier reported alkylation conditions[21] upon exposure to allylmagnesium chloride in presence of catalytic amounts of $ZnCl_2$ (Scheme 2). The corresponding *α*-methyl substituted *γ*,*δ*-unsaturated *tert*-butyl ester was furnished highly enantiospecific (91 % *ee*) with only a slight erosion in terms of enantioselectivity long in good yield. Reduction of latter mediated by lithium aluminium hydride and successive TBS-protection resulted in the silylated alcohol **12**. Next, the installation of the *Z*-configurated trisubstituted double bond present in **17** could be tackled by first catalytic hydroboration of **13**, followed by a subsequent boron-magnesium exchange reaction recently developed in our group[22] upon treatment with 1,4-di(chloromagnesium)butane to form the corresponding alkyl Grignard reagent and second by a Negishi coupling with the

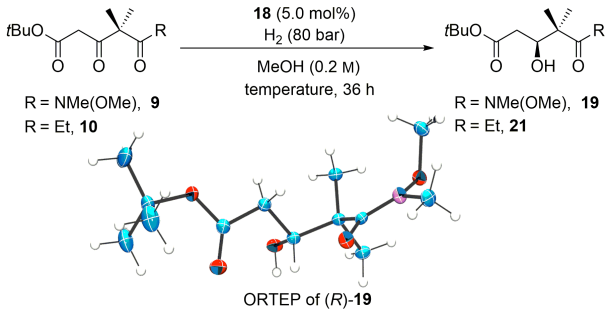


Scheme 3. Preparation of the southern fragment. Reagents and conditions: a) (*S*)-**18** (5.0 mol%), H_2 (30 bar), EtOH, 75 °C, 12 h, 99 %, 92 % ee (94 %, >99% ee after crystallization from cyclohexane); b) 2,6-lutidine, TBSOTf, CH_2Cl_2, -78 °C then room temperature, 7 h; c) aq. $NaHCO_3$, THF, room temperature, 16 h, 99 % (2 steps); d) EtMgBr, THF, 40 °C, 24 h, 89 %; e) (*S*)-**18** (5.0 mol%), H_2 (80 bar), MeOH, 10 °C, 36 h, 99 %, 86 % ee; f) TFA, CH_2Cl_2 0 °C then room temperature, 18 h, quant. (88 %, 96 % ee after crystallization from pentane/Et_2O); g) 2,6-lutidine, TBSOTf, CH_2Cl_2, -78 °C then room temperature, 7 h; h) aq. $NaHCO_3$, THF, room temperature, 16 h, quant. (2 steps).

literature known C3-linchpin **14**,[24] which was prepared highly stereoselectively from propyne within just one step. Emphasizing that palladium-catalyzed coupling reactions of alkenylboranes with alkyl halides in general tend to be less satisfactory than those of their corresponding iodoalkenyl counterparts, the vinylboronic acid ester **15** was converted to its vinyliodide analogue in excellent yield and subsequently subjected to the indicated cross-coupling conditions reported earlier for similar transformations,[25] leading to **17** in excellent yield which carried the desired trisubstituted *Z*-configurated double bond motif exclusively.[26] To this end, global TBS-deprotection was accomplished by treatment with TBAF and a subsequent Swern oxidation of the corresponding alcohol delivered the northern fragment **6** in overall 9 linear steps starting from **11**.

Hence, the next assignment concentrated on the preparation of the desired literature known southern fragment **8** (Scheme 3).[19] Although a step efficient and atom-economic synthesis of **8** seemed straightforward, we were surprised to find hardly any precedent. Instead, step lasting solutions using stoichiometric amounts of reagents, premetalated C-nucleophiles, chiral auxiliaries to install the required stereocenter prevail in literature. To circumvent this issue, we redesigned the approach to **8** by either starting from the 3-oxoglutaric acid derivative **9** or the *β*,*γ*-diketoester **10**, respectively, which both were exposed to Noyori hydrogenation conditions. Earlier investigations in the fields of selective asymmetrical hydrogenation of these types of substrates by Zhang[20a] and Carpentier[20b] resulted either in only moderate enantioselectivities, overreduction to the corresponding diol in terms of starting from **10**, the use of non-commercially available catalysts and an unspecified absolute configuration of the corresponding products. With this perspective, both pathways in order to obtain the southern fragment **8** either starting from **9** or **10** were reinvestigated. Following on from prior studies[20] we carried out initial reactivity assays with **9** in presence of catalytic amounts of (*R*)-**18** (5.0 mol%) as described in literature in EtOH at elevated temperatures (75 °C). We were pleased to discover that the

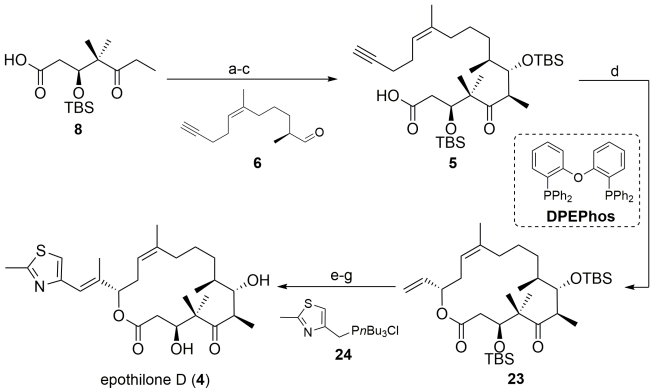
Table 1. Conditions for the enantioselective Noyori-type hydrogenation of the 3-oxoglutaric acid derivative **9** and the β,γ-dieketoester **10** (see Scheme 3).[a]



Entry	Substrate	Product	T [°C]	Yield [%][b]	*ee* [%][c]
1[d]	**9**	(*R*)-**19**	75 °C	89	92
2[e]	**9**	(*S*)-**19**	75 °C	99 (94)[f]	92 (99)[f]
3	**10**	**21**	RT	98	84
4	**10**	**21**	10	99	86
5	**10**	**21**	0	74	89
6	**10**	**21**	-10	17	95

[a] Reaction conditions: **10** (5.0 mmol), (*S*)-**18** (5.0 mol%) in 25 ml of MeOH, 36 h. [b] Cited yields are those isolated after silica gel chromatography. [c] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [d] Reaction conditions: **9** (5.0 mmol), (*R*)-**18** (5.0 mol%) in 25 ml of EtOH, 12 h. [e] Reaction conditions: **9** (5.0 mmol), (*S*)-**18** (5.0 mol%) in 25 ml of EtOH, 12 h. [f] After a single recrystallization.

reaction of **9** furnished the desired *β*-hydroxy ester both in good yield and highly enantioselective (92 % ee), albeit (*R*)-**19** possessing the opposite absolute configuration as determined by X-ray crystallographic analysis (Table 1, entry 1).[23] Hence, the product possessing the correct absolute configuration could be successfully obtained in gram-scale amounts and an excellent yield (99 %) by using equal reaction conditions but in presence of (*S*)-**18** (Table 1, entry 2). Gratifyingly, a single recrystallization of (*S*)-**19** furnished essentially enantiopure product in gram-scale quantities, which could then be transposed with only little extra synthetic efforts to the literature known southern fragment (**8**) first by TBS protection of the alcohol, alongside with a parallel deprotection and silylation of the carboxylic acid moiety, before being saponificated to the corresponding free carboxylic acid and next C2-elongated upon treatment with EtMgBr at slightly elevated temperatures (Scheme 3). Perpendicular to this when emanating from **10**, being already fully equipped in terms of the number of carbon atoms present in the skeleton, the Noyori hydrogenation of the posterior proved to be a challenging exercise. After screening numerous chiral bidentate binap-type bidentate diphosphine ligands, the reaction temperature was found to be most crucial for the outcome of this process in terms of obtained yields and enantioselectivites (Table 1; entries 3-6). To our delight, we were pleased to discover that the reaction worked well at lower temperatures (10 °C) using simple (*S*)-binap as the privileged ligand to afford the desired product **21** in both high yield (99 %) and decent enantioselectivities (86 % *ee*; Table 1, entry 4). After deprotection of the *tert*-butyl ester, the enantioselectivity could



Scheme 4. Completition of epothilone D. Reagents and conditions: a) LDA, **8**,THF, -78 °C to -40 °C, 1 h, quant., d.r. 1:1; b) 2,6-lutidine, TBSOTf, CH_2Cl_2, -78 °C then room temperature, 6 h; c) aq. $NaHCO_3$, THF, room temperature, 5 h, 97 % (2 steps; 49 % for **5**); d) [{Rh(cod)Cl}$_2$] (50 mol%), DPEPhos (100 mol%), benzoic acid (100 mol%), DCE, 70 °C, 72 h, 43 %, d.r. 4:1; e) $PdCl_2$ (50 mol%), 1,4-benzoquinone, DMF/H_2O (7:1), room temperature, 5 h, 71 %; f) KHMDS, THF, -78 °C to -20 °C, 2 h, 74 %; g) TFA, CH_2Cl_2, 0 °C, 1 h, 74 % (39 % over 3 steps).

further be enriched by recrystallization of the *β*-hydroxyacid to 96 % *ee* and in addition to this, the structure of **22** could be secured at this point by X-ray crystallographic analysis (Scheme 3).[23] A concluding TBS-protection paved the way to access the southern fragment **8** in less than five steps starting from **9** or **10**. At this juncture, we contemplated an aldol addition reaction to fuse both fragments **6** and **8**.[26] Conditions developed by Lin and co-workers[19a] in a similar approach of epothilone D to grant a highly diastereoselective addition reaction proved to be incompatible with the alkyne **6**, thus resulting in a complex product mixture. The price to pay in this particular application was the use of LDA-mediated conditions on the way to the *ω*-alkinyl-substituted carboxylic acid **5**,[19e] resulting in the corresponding addition product to be forged in an excellent overall yield, but unfortunately in analogy to previous syntheses of epothilone A-D[18,19] with a lack in the diastereoselectivity of the reaction (d.r. 1:1). After TBS-protection of the corresponding alcohol, both diastereomers could be separated accessing **5** in 49 % yield, along with its undesired diastereoisomer in 48 % yield. Next, after the lactonization precursor **5** was prepared for our intramolecular macrolactonization reaction, first reactivity assays encouraged us to screen numerous conditions and we were pleased to discover that the valuable interim structure **23** could be obtained in amendable 43 % yield[27] with good diastereoselectivity (d.r. 4:1) in the presence of [{Rh(cod)Cl}$_2$] (50 mol%), DPEphos (100 mol%) and benzoic acid (100 mol%) in DCE at 70 °C. Noteworthy is at this point that the newly generated stereocenter was selectively installed without the aid of a chiral ligand starting from alkynes, just by substrate control. For the further synthesis of epothilone D (**4**), a Tsuji-Wacker type oxidation reaction was elected to install the required ketone in the allylic side. Using reaction conditions recently reported by our group,[15b] **23** was smoothly oxidized to the corresponding ketone in presence of $PdCl_2$ and benzoquinone. Subsequent Wittig olefination conditions reported by Altmann and co-workers[28] for the synthesis of related compounds and a final overall deprotection finally led to epothilone D (**4**), exhibiting spectral properties identical in all respects to those reported for

the natural product.[18,19]

Overall, we have accomplished the total synthesis of epothilone D by an interaction of methodologies developed by our group, including a diastereoselective macrolactonization strategy, the use of our reported zinc-catalyzed cross-coupling of α-hydroxy ester triflates with Grignard reagents and furthermore the application of our hydroboration/boron-magnesium exchange sequence. The conclusion drawn from this ultimately successful total synthesis project, invigorates our parallel efforts to elaborate a general enantioselective approach to macrocycles by starting from ω-alkinyl-substituted carboxylic acids as well as its further application in complex target molecule synthesis.

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Keywords: alkynes • rhodium • macrocycles • total synthesis • natural products

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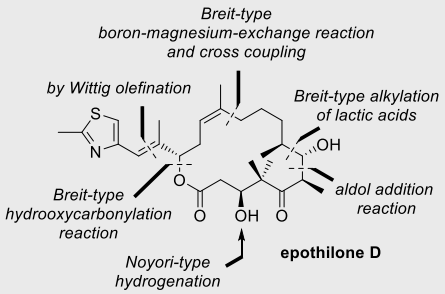

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The Total Synthesis of Epothilone D as a Yardstick for Probing New Methodologies

The natural product family of the epothilones are one of countless natural products holding macrolactones in their often very complex structural motif. An interaction of methodologies developed by our group, including a diastereoselective macrolactonization, the use of our reported zinc-catalyzed cross-coupling of *α*-hydroxy ester triflates with Grignard reagents and the application of our hydroboration/boron-magnesium exchange sequence allows for rapid access to this fascinating natural product.