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Concise total syntheses of epothilone A and C based on alkyne metathesis

Alois Fürstner,* Christian Mathes and Karol Grela

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany. E-mail: fuerstner@mpi-muelheim.mpg.de; Fax: ++49 208 306 2994; Tel: ++49 208 306 2342

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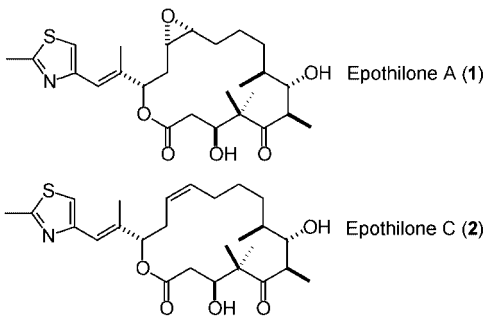
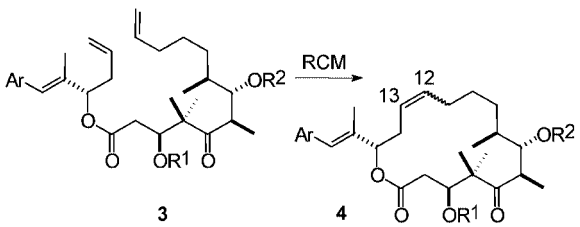
A ring closing alkyne metathesis reaction catalyzed by the molybdenum complex 26 followed by a Lindlar reduction of the resulting cycloalkyne product opens an efficient and stereoselective entry into epothilone A and C.

The discovery that epothilone A (**1**)[1] and congeners share a common mechanism of action with paclitaxel (Taxol®) in triggering programmed cell death (apoptosis) and exert high activity even against paclitaxel-resistant human cancer cell lines *in vitro* has spurred considerable drug development programs worldwide.[2] As a consequence, these compounds became the focal point of many preparative studies aiming at their total synthesis as well as at a synthesis-driven mapping of the structure–activity relationship of these promising natural products.[2,3]



In this context it is remarkable that the first three successful approaches towards **1** were all based on ring closing alkene metathesis (RCM) for the formation of the 16-membered ring. Product **4** thus formed can be selectively epoxidized at the $\Delta^{12,13}$-bond and hence constitutes an excellent precursor for epothilone A.[4–6]



Although these studies were early highlights showing the enormous potential of RCM for advanced organic synthesis,[7] they *invariably suffered from the fact that there was little—if any—selectivity in favor of the required (Z)-alkene* **4** (Table 1). As this serious problem arose only towards the very end of rather laborious sequences and since the isomeric alkenes could not be readily separated at this stage, it is hardly surprising that subsequent total syntheses of **1** were largely based on strategies other than RCM that ensure better control over all structural elements of this target.[8]

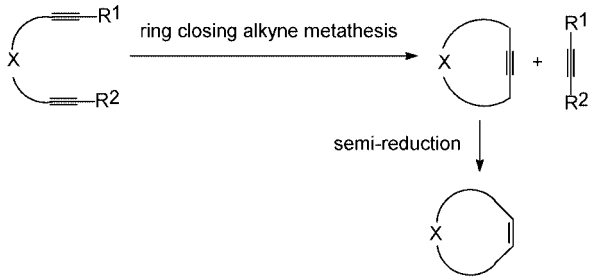
Recently, our group was able to show that the ring closing metathesis of *diynes* constitutes a promising alternative that retains all the advantages of metathetic conversions† but allows for the first time the gearing of the stereochemical issue to the cyclization event.[9] If combined with a Lindlar-type reduction, this method opens a *stereoselective entry into (Z)-alkenes* (Scheme 1). We felt that epothilone A constitutes an ideal testing ground for the scope of this emerging new methodology (Scheme 2).[9–11] Described below is the successful reduction of this plan to practice.

Table 1 RCM approaches towards epothilone A and C: formation of (*E*,*Z*)-mixtures (Ar = 2-methyl-4-thiazolyl)

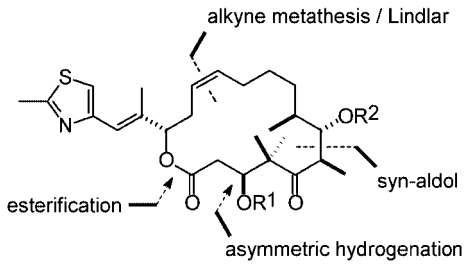
Catalyst[a]	R^1	R^2	Yield	*Z*:*E*	Ref.
[Ru]	TBS	TBS	86%	1.7:1	4*b*
	TBS	TBS	94%	1:1	6*a*
	TBS	H	85%	1.2:1	5*b*
	H	H	65%	1:2	4*b*
[Mo]	TBS	TBS	86%	1:2	4*b*

[a] [Mo] = Mo(=NAr)(=CHCMe$_2$Ph)[OCMe(CF$_3$)$_2$]$_2$; [Ru] = (PCy$_3$)$_2$(Cl)$_2$-Ru=CHPh.

Earlier studies had revealed that the selectivity gained in the formation of the three contiguous stereocenters at C-6, C-7 and C-8 by an aldol reaction strongly depends on the remote functionalization of the enolate partner.[2,3] The best results were reported by Schinzer *et al*. who employed ethyl ketone **11** bearing a conformationally rigid and chelating 1,3-dioxane unit as control element for this purpose.[6] We took recourse to this



Scheme 1 Stereoselective synthesis of (*Z*)-alkenes by ring closing alkyne metathesis/Lindlar reduction.



Scheme 2 Retrosynthetic analysis of epothilone C (**2**).

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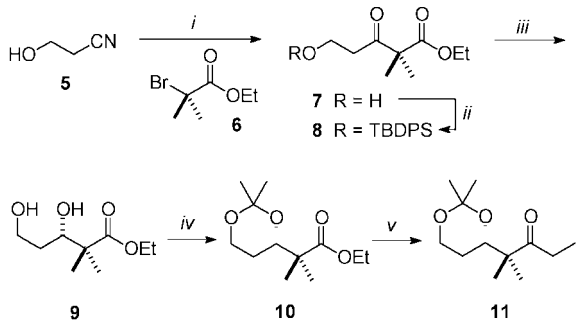
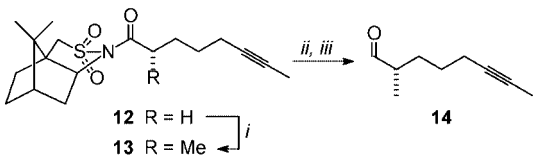
elegant solution, seeking, however, an improved and shorter entry into the required key building block **11**.

Our synthesis starts from commercially available 3-hydroxypropionitrile **5** which reacts with the zinc enolate derived from bromo ester **6** to afford ketoester **7** in 71% yield on a multigram scale (Scheme 3). This Reformatsky-type reaction is best carried out with the assistance of ultrasound.[12] Silylation of **7** with *tert*-butyldiphenylsilyl chloride under standard conditions followed by an asymmetric hydrogenation of **8** catalyzed by [((*S*)-binap)$RuCl_2$](NEt_3) in the presence of Dowex (H-form) to ensure acidic conditions delivers the unprotected diol **9** in high enantiomeric purity (ee = 94%).[13]‡ All attempts to perform the reduction directly with the unprotected substrate **7** resulted in rather poor conversion. Acetalization of **9** followed by reaction of the resulting product **10** with EtMgBr in toluene in the presence of NEt_3 affords compound **11** in excellent overall yield. The presence of the base during the addition of the Grignard reagent to the ester is essential, as it enolizes the ketone primarily formed and thereby avoids the formation of the corresponding tertiary alcohol by addition of a second equivalent of EtMgBr.[14]



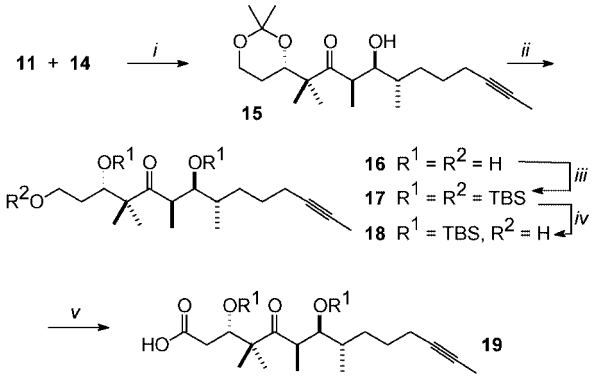
Scheme 3 *Reagents and conditions*: i, Zn, ultrasound, THF; then aq. HCl, 71%; ii, TBDPSCl, imidazole, DMF, 90%; iii, [((*S*)-binap)$RuCl_2$](NEt_3) (6 mol%), H_2 (65 bar), Dowex, EtOH, 80 °C, 71%; iv, 2,2-dimethoxypropane, acetone, camphorsulfonic acid cat., 92%; v, EtMgBr, NEt_3, toluene, 70 °C, 68%.

Having secured an improved access to this key building block, the subsequent aldol reaction was carried out in close analogy to that described by Schinzer *et al.*[6] The required aldehyde component **14** is readily formed as shown in Scheme 4, exploiting the excellent facial guidance exerted by Oppolzer's bornane sultam in the alkylation of substrate **12** (d.r. = 96:4).[15] Reaction of the lithium enolate derived from **11** with compound **14** affords aldol **15** in 70% yield (Scheme 5). The selectivity for the desired *anti*-Cram product was 7:1 (HPLC), which is easily separated from the minor isomer by flash chromatography. Further elaboration of this compound involving deprotection of the acetal, per-silylation of the resulting triol **16**, and regioselective cleavage of the primary TBS-ether in **17** is performed in analogy to literature routes.[5,6] Oxidation of the resulting alcohol **18** with PDC in DMF smoothly affords the desired carboxylic acid **19** ready for esterification with a suitable thiazol fragment.

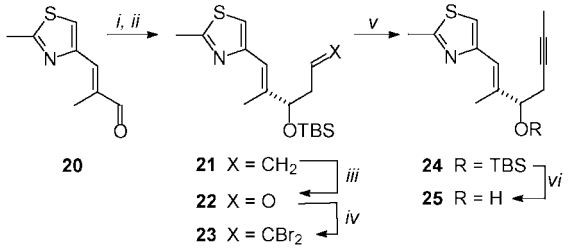


Scheme 4 *Reagents and conditions*: i, n-BuLi, THF–HMPA, MeI, −78 → −60 °C, 94%; ii, $LiAlH_4$, THF, 85%; iii, Pr_4NRuO_4 cat., NMO, CH_2Cl_2, MS 4 Å, 90%.

The preparation of the latter (Scheme 6) starts with an allylation of aldehyde **20** with (+)-Ipc_2B(allyl) as described earlier,[5] followed by silylation of the crude material with TBSCl and imidazole, thus delivering the homoallyl alcohol derivative **21** in 89% yield over both steps in excellent enantiomeric excess



Scheme 5 *Reagents and conditions*: i, LDA, THF, −78 °C, 70%; ii, PPTS, MeOH, 85%; iii, TBSOTf, 2,6-lutidine, 92%; iv, camphorsulfonic acid cat., CH_2Cl_2–MeOH (1:1), 78%; v, PDC, DMF, 83%.

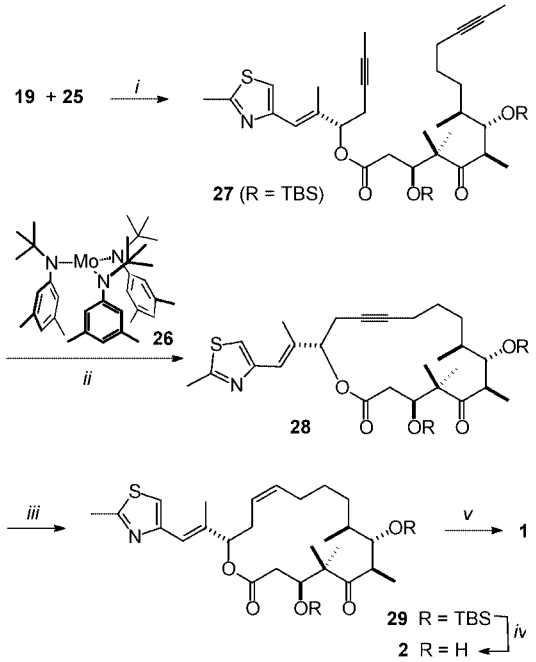


Scheme 6 *Reagents and conditions*: i, (+)-Ipc_2B(allyl); ii, TBSCl, imidazole, DMF, 89% (over both steps); iii, (1) OsO_4 cat., NMO; (2) $Pb(OAc)_4$, 86%; iv, CBr_4, PPh_3, CH_2Cl_2, 68%; v, *n*-BuLi, MeI, THF, 65%; vi, TBAF·$3H_2O$, THF, 74%.

(ee > 97%). Oxidative cleavage of its terminal double bond affords the somewhat unstable aldehyde **22** which is immediately used for a subsequent Corey-Fuchs reaction.[16] Specifically, treatment of **22** with CBr_4 and PPh_3 gives the expected 1,1-dibromo derivative **23**,[2c] which is converted into alkyne **24** by means of *n*-BuLi in THF and trapping of the acetylide anion thus formed with MeI. Desilylation under standard conditions followed by esterification of the resulting alcohol **25** with compound **19** sets the stage for the crucial macrocyclization step. It should also be noted that all attempts to form product **25** from aldehyde **20** by direct asymmetric propargylation were unrewarding in terms of yield and optical purity.

We were pleased to see that diyne **27** is in fact smoothly converted into the 16-membered cycloalkyne **28** in 80% isolated yield on exposure to catalytic amounts of the molybdenum amido complex **26**[17] in toluene–CH_2Cl_2 at 80 °C (Scheme 7). This outcome is particularly noteworthy as it compares well to the results obtained in the conventional RCM approaches (Table 1) in terms of yield and reaction rate. Furthermore, it clearly attests to the mildness and preparative relevance of the method since (i) neither the basic N-atom nor the sulfur group of the thiazole ring interfere with the catalyst, (ii) the labile aldol substructure, the rather electrophilic ketone, as well as the ester- and silyl ether groups are fully preserved, (iii) no racemization of the chiral center α to the carbonyl is encountered, and (iv) the rigorous chemoselectivity of the catalyst is confirmed, which reacts smoothly with alkynes but leaves pre-existing alkene moieties unaffected.§ Therefore, this particular example in concert with the previous applications from our laboratory[9–11] substantiates the notion that alkyne metathesis in general holds great promise for target oriented synthesis.

Lindlar reduction of cycloalkyne **28** followed by cleavage of the silyl ether groups in the resulting (*Z*)-alkene **29** by means of aq. HF in Et_2O–MeCN as the reaction medium delivers epothilone C **2** in 79% yield. Because the selective epoxidation of **29** has already been described by various groups,[2–6] this approach also constitutes a formal total synthesis of epothilone A **1**.



Scheme 7 *Reagents and conditions*: i, DCC, DMAP, CH_2Cl_2, 81%; ii, **26** (10 mol%), toluene–CH_2Cl_2, 80 °C, 8 h, 80%; iii, Lindlar catalyst, quinoline, H_2 (1 atm), CH_2Cl_2, quant.; iv, aq. HF, Et_2O–MeCN, 79%; v, dimethyldioxirane, 70% (ref. 4).

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Notes and references

† For a discussion of the strategic advantages of metathesis in general over more conventional transformations see ref. 18.

‡ The need to perform this reduction under slightly acidic conditions determines the choice of the protecting group for the primary alcohol; the TBDPS group turned out to be optimal, whereas the TBS ether was found to be too unstable.

§ Other available catalysts for alkyne metathesis are (i) $Mo(CO)_6$–*p*-chlorophenol and (ii) alkylidyne complexes such as $(t\text{-}BuO)_3W{\equiv}CCMe_3$. System (i), however, requires very harsh conditions (≥130 °C), whereas the tungsten alkylidyne is sensitive towards basic nitrogen atoms or sulfur(II) groups in the diyne substrate. Therefore they are not appropriate for the cyclization of **27** to **28**. For a more detailed discussion see ref. 11*a*.

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