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Total Synthesis

Catalysis-Based Total Synthesis of Putative Mandelalide A**

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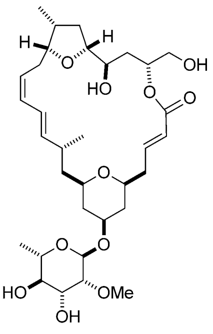
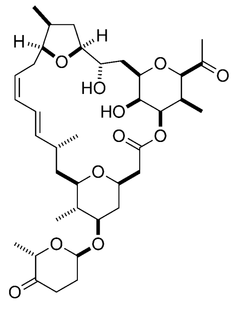
***Abstract:** A concise synthesis of the putative structure assigned to the highly cytotoxic marine macrolide mandelalide A (**1**) is disclosed. Specifically, an iridium-catalyzed two-directional Krische allylation and a cobalt-catalyzed carbonylative epoxide opening served as convenient entry points for the preparation of the major building blocks. The final stages feature the first implementation of terminal-acetylene metathesis into natural product synthesis, which is remarkable as this class of substrates was beyond reach until very recently; key to success was the use of the highly selective molybdenum alkylidyne complex **42** as the catalyst. Although the constitution and stereochemistry of the synthetic samples are unambiguous, the spectra of **1** as well as of 11-epi-**1** deviate from those of the natural product, which implies a subtle but deep-seated error in the original structure assignment.*

The supply of meaningful amounts of promising bioactive compounds that are basically inaccessible from the source organism is increasingly recognized as a prime task of contemporary natural product synthesis.[1] Many secondary metabolites of marine origin fall into this category. This notion is exemplified by the mandelalides, a small family of (glycosylated) macrolides that are derived from a rare South African ascidian of the *Lissoclinum* genus.[2] Although preliminary data indicate impressive in vitro cytotoxicity against human NCI-H460 lung cancer and mouse Neuro-2A neuroblastoma cell lines,[3] a systematic survey could not be carried out with the available minute sample (800 μg).[2]

Mandelalide A (**1**) shows considerable structural homology to madeirolide A (**2**), an equally scarce metabolite, which was isolated from a marine *Leiodermatium* sponge.[4,5] Interestingly though, **2** exhibited no appreciable antiproliferative activity against two pancreatic cancer cell lines.[6] Even if one takes the differences in the bioassays into account, these somewhat conflicting results raise questions as to possible structure–activity relationships and certainly advocate closer inspection.



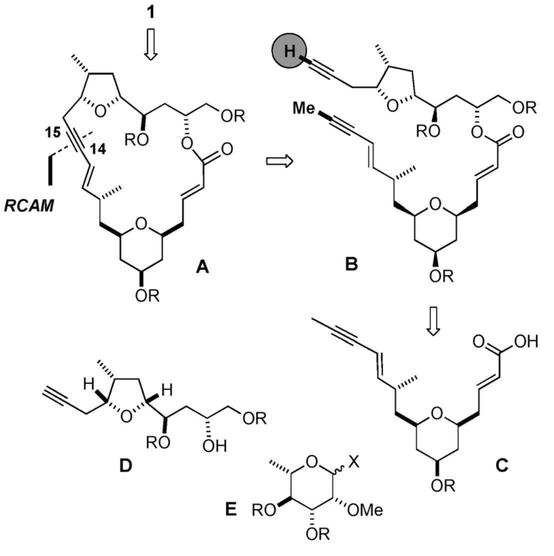
Mandelalide A (**1**)
(proposed structure)



Madeirolide A (**2**)

As a quintessential first step, we pursued the total synthesis of mandelalide A (**1**) as the most active member of the series. In the quest for a practical solution, we saw an excellent opportunity to scrutinize catalytic methods that have been developed in our laboratory (Scheme 1). Previous experience suggests that a sequence of ring-closing alkyne metathesis (RCAM)[7,8] followed by semi-reduction of the resulting cycloalkyne **A** should allow the macrocyclic frame of **1** to be forged with excellent selectivity at the *Z*-configured C14–C15 olefin site.[9] Although the latest generation of catalysts that are based on molybdenum alkylidynes with triphenylsilanolate ligands is expected to cope with the polar functionality that is presented by the envisaged cyclization precursor of type **B**,[10] the virtues of these catalysts can be probed in an unorthodox but particularly stringent way by variation of the substituents on the alkyne termini.

Alkyne metathesis, as it stands today, largely relies on the use of internal acetylene derivatives, because terminal alkynes are prone to rapid polymerization on contact with



Scheme 1. Retrosynthetic analysis of mandelalide A (**1**) based on ring-closing alkyne metathesis (RCAM) of a precursor containing one internal and one terminal acetylene.

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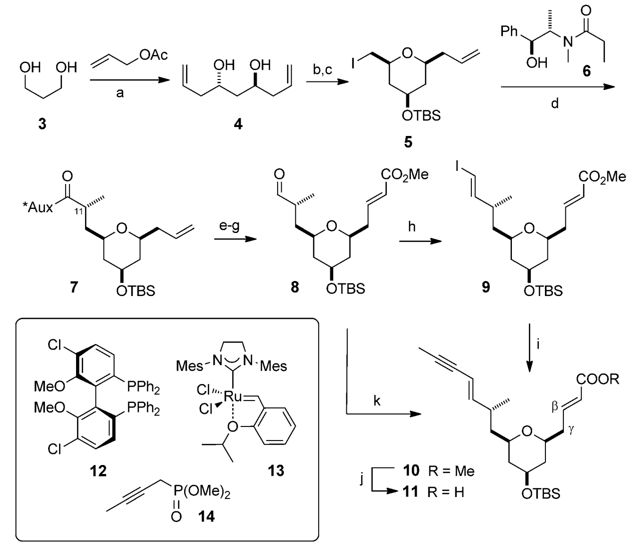
a Schrock alkylidyne.[7] From the synthetic vantage point, however, their use is desirable as they are often accessible in fewer steps. The first successful metathesis reactions of terminal alkynes have been reported only very recently using catalysts with barely basic ancillary ligands.[11,12] Yet, attempted ring closure of di-terminal diyne substrates gave variable outcomes, which might be explained, at least in part, by the particular constraints of macrocyclization; in contrast, reactions of substrates that comprise one terminal and one internal alkyne seem to be more robust.[12] However, all available information derives from a small set of simple model compounds, and this tactic definitely needs further validation. The mandelalide case, invoking an elaborate cyclization precursor of type **B**, provides a compelling test.

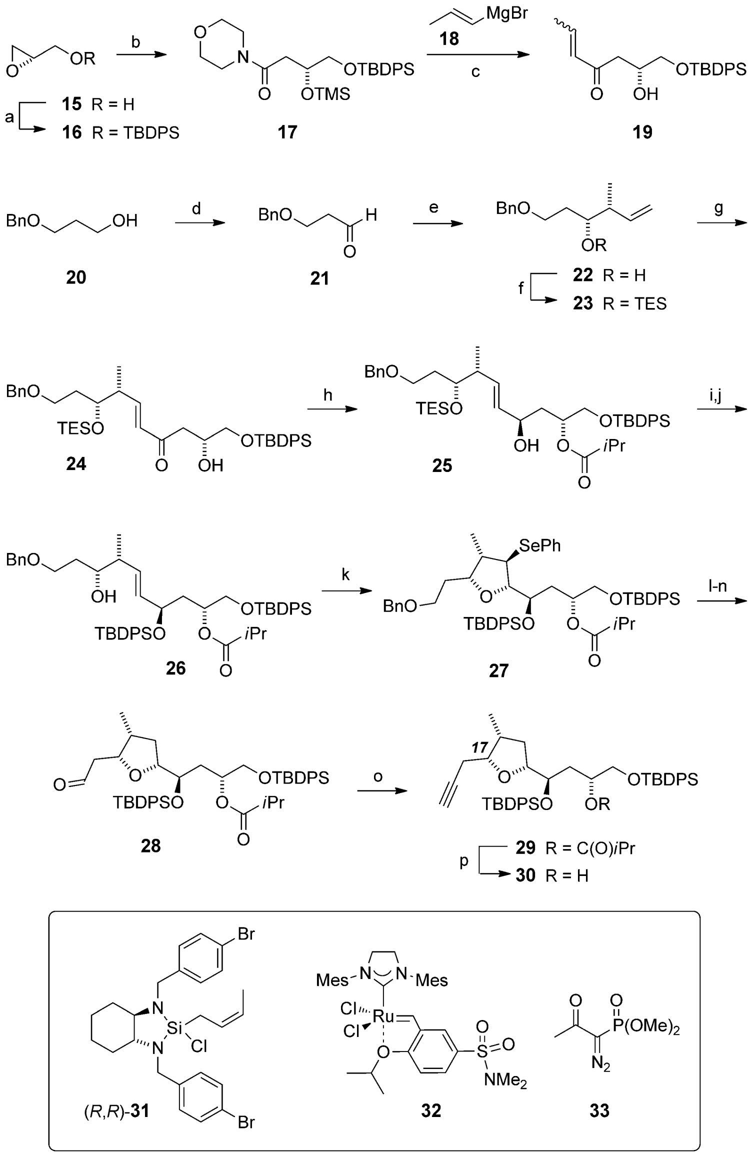
The required acid sector **C** was readily prepared from propane-1,3-diol (Scheme 2). An iridium-catalyzed two-directional Krische allylation furnished multigram amounts of the known C_2-symmetric diol **4** with exquisite levels of diastereo- and enantioselectivity and hence served as a practical entry point.[13] Desymmetrization by iodoetherification followed by TBS protection afforded alkyl iodide **5**,[14] which was reacted with the lithium enolate of **6**. Although somewhat forcing conditions were needed for this alkylation to proceed, the methyl-branched chiral center was set with impeccable selectivity (d.r. = 97:3).[15] Reductive cleavage of the auxiliary preceded chain extension by cross metathesis with methyl acrylate.[16] Subsequent oxidation of the primary alcohol terminus led to the corresponding aldehyde **8**, which was exposed to the lithium anion of **14** to give the desired enyne **10**. The yield, however, was modest and variable and could not be improved, despite considerable experimentation. Therefore, aldehyde **8** was first subjected to a Takai olefination[17–19] to give alkenyl iodide **9**, which was amenable to a modified Suzuki propynylation;[20] this reliable sequence was much better suited for material throughput. Somewhat unexpectedly though, the saponification of the methyl ester in **10** gave rather complex mixtures; best results were obtained with Me_3SiOK in Et_2O, although partial deconjugation of the double bond could not be avoided even under these mild conditions (ca. 8%). This outcome, albeit a slight complication with respect to product characterization, was inconsequential and could be rectified prior to macrocyclization (see below).



Scheme 2. a) $[Ir(cod)Cl]_2$ (5 mol%), **12** (10 mol%), 3-nitro-4-chlorobenzoic acid (20 mol%), Cs_2CO_3, 1,4-dioxane, 90°C, 71% (d.r. ≥ 29:1, 99% *ee*); b) I_2, $NaHCO_3$, MeCN, −40°C, 81% (d.r. = 5:1); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 96%; d) LDA, LiCl, THF, 0°C→45°C, 76% (d.r. = 97:3); e) LDA, $BH_3{\cdot}NH_3$, THF, 0°C→RT, 96%; f) methyl acrylate, **13** (3 mol%), CH_2Cl_2, 83% (+ 7% of the *Z*-isomer); g) Dess–Martin periodinane, CH_2Cl_2, 0°C→RT, 77%; h) CHI_3, $CrCl_2{\cdot}THF$, THF, −8°C, aq. serine work-up, 72% (+8% of the *Z*-isomer); i) propynyl sodium, $B(OMe)_3$, $[Pd(dppf)Cl_2]{\cdot}(CH_2Cl_2)$ (10 mol%), THF, 70°C, 81%; j) Me_3SiOK, Et_2O, 80% (+7% of the β,γ-isomer); k) **14**, LiHMDS, THF, −78°C, 41–54% (*E*/*Z* = 7:1). Aux* = (1*S*,2*S*)-2-(methyl-λ^2-azanyl)-1-phenylpropan-1-ol, cod = 1,5-cyclooctadiene, dppf = 1,1′-bis(diphenylphosphino)ferrocene, LDA = lithium diisopropylamide, LiHMDS = lithium hexamethyldisilazide, Mes = 2,4,6-trimethylphenyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

The second major building block **D** was prepared as shown in Scheme 3. Silylation of commercially available **15** followed by cobalt-catalyzed carbonylative epoxide opening in the presence of *N*-(trimethylsilyl)morpholine opened a convenient entry into amide **17**, which reacted with 1-propenylmagnesium bromide (**18**) to give enone **19** in good overall yield.[21,22] In parallel, the terminal alkene **23** was prepared by a copper/TEMPO-co-catalyzed air oxidation of **20**[23] followed by scandium triflate catalyzed crotylation of the resulting aldehyde **21** with the chlorosilane donor **31**. As expected, this reaction was distinguished by excellent diastereo- and enantioselectivity in favor of the *syn*-configured product **22** (d.r. = 98:2, 94% *ee*).[24] Cross-metathesis of the derived TES ether **23** with enone **19** worked best using complex **32** as the catalyst.[25] A SmI_2-catalyzed Evans–Tishchenko reaction of product **24** with an excess of *i*PrCHO set the *anti*-configured 1,3-diol motif while discriminating the two alcohol groups at the same time.[26,27]

Compound **25** thus formed was swiftly elaborated into the homoallylic alcohol **26** as an adequate precursor for the signature tetrahydrofuran motif yet to be closed. A brief screening of several conceivable $[I^+]$ or $[PhSe^+]$ sources suggested that a selenoetherification under acidic conditions was most promising, provided the system was operated in the presence of a catalytic Lewis base activator.[28] Specifically, treatment of **26** with a slight excess of *N*-(phenylselenyl)phthalimide and trifluoroacetic acid in the presence of catalytic amounts of $Ph_3P{=}S$ in CH_2Cl_2 at low temperature furnished product **27** in high yield and excellent selectivity (d.r. = 14:1). Attempted deselenation over Raney Ni with concomitant cleavage of the terminal benzyl ether gave erratic results. Therefore, this compound was first subjected to deselenation under free-radical conditions followed by hydrogenolysis of the benzyl ether over Pearlman's catalyst. The resulting alcohol was oxidized to give the rather sensitive aldehyde **28**. Although treatment with diazophosphonate **33** under standard conditions (K_2CO_3, MeOH)[29] provided alkyne **29**, substantial epimerization at the C17 position through a retro-oxa-Michael/Michael process was noticed. Gratifyingly, this stereochemical erosion could be suppressed by activation of **33** with NaOMe in THF prior to addition of the aldehyde at low temperature.[30] The terminal alkyne **30** thus formed was meant to serve in the projected alkyne metathesis



Scheme 3. a) TBDPSCl, imidazole, CH_2Cl_2, 0°C→RT, 94%; b) $[Co_2(CO)_8]$ (8 mol%), CO (1 atm), *N*-(trimethylsilyl)morpholine, EtOAc, 74%; c) **18**, THF, −25°C (acidic quench at −78°C), 83% (*E*/*Z* = 2:1); d) $[Cu(MeCN)_4]BF_4$ (5 mol%), 2,2′-bipyridine (5 mol%), TEMPO (5 mol%), *N*-methylimidazole (10 mol%), MeCN, air, 94%; e) (*R*,*R*)-**31**, $Sc(OTf)_3$ (5 mol%), CH_2Cl_2, −78°C→0°C, 82% (d.r. = 98:2, 94% *ee*); f) TESCl, Et_3N, DMAP, CH_2Cl_2, 0°C→RT, 90%; g) **19**, **32** (8 mol%), CH_2Cl_2, reflux, 79%; h) *i*PrCHO, SmI_2 (35 mol%), THF, −50°C, 78% (d.r. > 19:1); i) TBDPSCl, imidazole, CH_2Cl_2, 0°C→RT, 87%; j) camphorsulfonic acid (30 mol%), CH_2Cl_2/MeOH (2:1), 0°C, 97%; k) *N*-(phenylselenyl)phthalimide, trifluoroacetic acid, $Ph_3P{=}S$ (12 mol%), CH_2Cl_2, −40°C→−20°C, 83% (d.r. = 14:1); l) Bu_3SnH, AIBN, toluene, 80°C, 93%; m) $Pd(OH)_2/C$ (cat.), H_2 (1 atm), EtOH/EtOAc (9:1), 88%; n) Dess–Martin periodinane, CH_2Cl_2, 0°C→RT, 91%; o) **33**, MeONa, THF, −78°C; then **28**, −78°C→−50°C, 93% (d.r. ≥ 98:2); p) Dibal-H, toluene, −78°C, 97%. AIBN = azobis(isobutyronitrile), Dibal-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, TBDPS = *tert*-butyldiphenylsilyl, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy radical, TES = trimethylsilyl, TMS = trimethylsilyl.

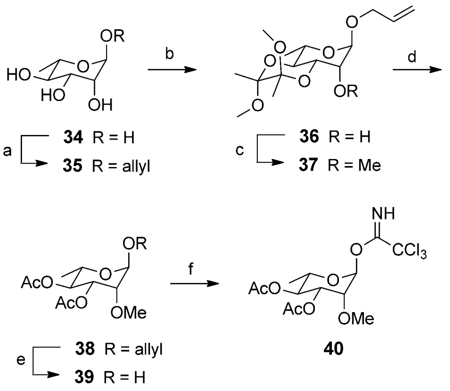
reaction.[31] Finally, the isobutylester in **29** was cleaved with Dibal-H rather than by hydrolysis to avoid scrambling of the silyl protecting groups.

The yet missing rhamnosyl segment **E** was prepared by protection of the two equatorial hydroxy groups of allyl rhamnoside **35** as the 1,2-diacetal **36**,[32] methylation of the remaining alcohol, and exchange of the bisketal in **37** for two acetyl groups to give product **38** (Scheme 4). Oxidative cleavage of the allyl moiety[33] followed by installation of an anomeric trichloroacetimidate afforded product **40** as an adequate glycosyl donor.[34]

With appreciable amounts of all fragments in hand, the project entered the crucial assembly phase in which the macrocyclic perimeter of mandelalide A had to be forged (Scheme 5). The seemingly routine esterification of acid **11** with alcohol **30** was surprisingly challenging. DCC gave the best results amongst the host of activating agents investigated, although the reaction was accompanied by substantial isomerization of the enoate double bond out of conjugation. This problem could be fixed upon treatment of the resulting mixture with catalytic amounts of DBU in MeCN at 50°C.[35] In striking contrast, the macrocyclization of diyne **41** proceeded with remarkable ease even at ambient temperature when catalyzed by molybdenum alkylidyne **42** as the arguably most active and selective catalyst for alkyne metathesis currently available;[10] the reaction was performed in the presence of molecular sieves to sequester the released propyne. In view of the dense decoration of **41** with polar substituents and the fact that it comprises a challenging terminal alkyne unit, which was beyond reach of RCAM until recently, the outcome attests to the maturity of this method.[7]

Activated Zn(Cu/Ag) in protic medium served the semi-reduction of **43** to the corresponding *E*,*Z*-diene very well.[36] Slightly acidic conditions then allowed the TBS ether to be cleaved without touching the more robust TBDPS groups, which hence set the stage for the attachment of the saccharide. As expected, the TESOTf-catalyzed rhamnosylation of **44** was productive and selective alike.[37] Finally, global deprotection of the resulting product **45** was achieved by careful saponification of the acetate groups followed by cleavage of the remaining silyl ethers with HF·pyridine in THF/pyridine. These buffered conditions were the only way to effect this final step in good yield even though a variety of other reagents was screened; however, these either failed to remove the shielded secondary TBDPS ether and/or led to significant ring expansion by migration of the lactone acyl group onto the emerging primary alcohol site.

Overall, this concise route is deemed quite satisfactory, not least because the majority of the constructive operations are catalytic in nature (21 steps, longest linear sequence; ca. 4.5% overall yield), and more than 20 mg of **1** were made available in this first round. The spectroscopic signatures of the synthetic samples leave no doubt about the constitution and stereochemistry of the material; regrettably though, comparison with the data of the natural product revealed small but



Scheme 4. a) Allyl alcohol, H_2SO_4 (cat.), reflux, 78 %; b) butane-2,3-dione, $MeC(OMe)_3$, pTsOH·H_2O (cat.), MeOH, reflux, 72 %; c) NaH, MeI, DMF, 0 °C→RT, 64 %; d) i) trifluoroacetic acid/H_2O (20:1); ii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C→RT, 68 %; e) SeO_2, HOAc, 1,4-dioxane, reflux, 86 %; f) Cl_3CCN, Cs_2CO_3, CH_2Cl_2, 98 %. pTs = *para*-toluenesulfonyl.

distinct differences. The largest deviations in the ^{13}C NMR spectra were observed for the C11 carbon atom ($\Delta\delta = +1.4$ ppm) and the attached C25 methyl branch ($\Delta\delta = -1.8$ ppm). Furthermore, the recorded coupling constant ($^3J_{11,12} = 7.6$ Hz) is not in accordance with that of the natural product (9.6 Hz). The configuration of this chiral center had been assigned by the isolation team based on ROESY data and the analysis of the homo- and heteronuclear coupling constants.[2] As the macrocycle of mandelalide A is fairly flexible, and the data hence necessarily represent an average over more than one conformation, it seemed reasonable to assume that this site might be a locus of stereochemical misassignment. Moreover, handheld models of the compound with the opposite configuration at the C11 position suggested that this isomer might also adopt a conformation that matches the experimentally observed ROESY contacts and *J* coupling patterns. To verify this hypothesis, 11-*epi*-**1** was prepared by following the same assembly route but using the enantiomeric Myers auxiliary[15] in the alkylation step that sets the chiral center in question.[38] Much to our dismay, the spectral data of 11-*epi*-**1** deviate from those of the natural product to a similar extent. Interestingly, however, the recorded coupling constant ($^3J_{11,12} = 9.7$ Hz) now fits the one of mandelalide A very well, which possibly indicates more than one misassignment in the originally proposed structure.

Therefore, we conclude that the error made by the isolation team is subtle but profound, and a considerable effort will be necessary to solve the riddle.[39] We (and many others) have experienced such frustrating situations surprisingly often in the recent past.[40,41] Somewhat ironically, they remind us that contemporary natural product total synthesis does not only serve the supply management alluded to in the introduction; all too often it is needed, even in the age of ever more sophisticated spectroscopy, to decide on structural issues.[42]

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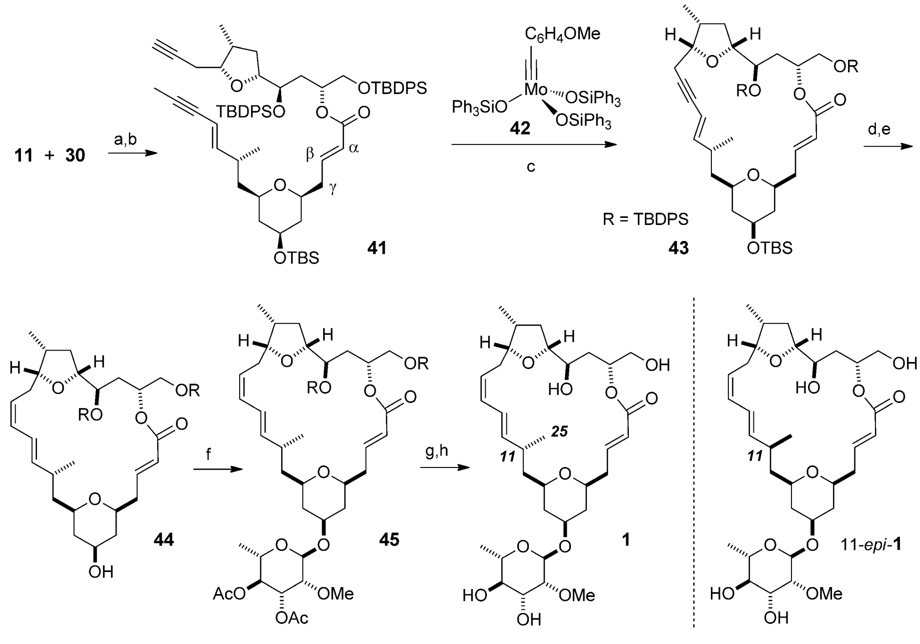
Keywords: alkyne metathesis · molybdenum · natural products · structure elucidation · total synthesis



Scheme 5. a) DCC, DMAP, CH_2Cl_2, 64 % (α,β/β,γ isomers = 1.5:1); b) DBU (25 mol %), MeCN, 50 °C, 91 %; c) **42** (10 mol %), M.S. (4 Å and 5 Å), toluene, 72 %; d) Zn(Cu/Ag), THF/MeOH/H_2O (1:1:1), 45 °C, 88 %; e) pTsOH·H_2O (cat.), CH_2Cl_2/MeOH (2:1), 90 %; f) **40**, TESOTf (30 mol %), CH_2Cl_2, M.S. (4 Å), −50 °C, 89 %; g) K_2CO_3, MeOH, 0 °C, 80 %; h) HF·pyridine, pyridine, THF, 0 °C→RT, 80 %. DCC=*N*,*N'*-dicyclohexylcarbodiimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, M.S. = molecular sieves.

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[38] A Scheme showing the entire route is contained in the Supporting Information; note, however, that not all steps leading to 11-*epi*-**1** were fully optimized.

[39] A comparison of **1** and **2** shows that their "northern" stereoclusters, which comprise the tetrahydrofuran ring, are enantiomeric; one may be tempted to speculate that this entire domain has been misassigned in **1**.

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[41] a) A. Larivée, J. B. Unger, M. Thomas, C. Wirtz, C. Dubost, S. Handa, A. Fürstner, *Angew. Chem.* **2011**, *123*, 318–323; *Angew. Chem. Int. Ed.* **2011**, *50*, 304–309; b) P. Buchgraber, T. N. Snaddon, C. Wirtz, R. Mynott, R. Goddard, A. Fürstner, *Angew. Chem.* **2008**, *120*, 8578–8582; *Angew. Chem. Int. Ed.* **2008**, *47*, 8450–8454; c) A. Kondoh, A. Arlt, B. Gabor, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 7731–7738; d) A. Fürstner, L. C. Bouchez, L. Morency, J.-A. Funel, V. Liepins, F.-H. Porée, R. Gilmour, D. Laurich, F. Beaufils, M. Tamiya, *Chem. Eur. J.* **2009**, *15*, 3983–4010; e) A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069; for a correction of a putative bioactivity with the help of synthetic material, see: f) K. Micoine, P. Persich, J. Llaveria, M.-H. Lam, A. Maderna, F. Loganzo, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 7370–7383.

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