

Published in final edited form as:

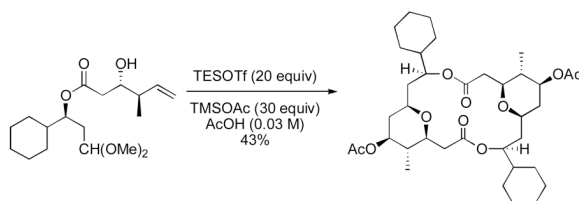
Org Lett. 2009 November 19; 11(22): 5342–5345. doi:10.1021/ol9022062.

Symmetric Macrocycles by a Prins Dimerization and Macrocyclization Strategy

Michael R. Gesinski, Kwanruthai Tadpetch, and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025

Abstract



A tandem dimerization/macrocyclization reaction utilizing the Prins cyclization has been developed. This reaction develops molecular complexity through the formation of highly substituted dimeric tetrahydropyran macrocycles. Mild conditions utilizing rhenium(VII) catalysts were explored for aromatic substrates while harsher Lewis acidic conditions were used for aliphatic substrates. Both aldehydes and acetals are shown to be viable substrates for this reaction.

Oxacyclic macrodimers are an important class of natural products that offer a wide array of structural complexity and bioactivity.¹ These macrolides have become popular targets for synthetic chemists.² The most direct way to construct these molecules is through the union of two monomeric species in a tandem dimerization and macrocyclization reaction. The most common version of this strategy utilizes two esterification reactions between an activated acid and an alcohol, the initial dimerization followed by a macrolactonization.³ While often successful, this approach does not greatly enhance the complexity of the intermediate through the formation of carbon-carbon bonds. Alternative bond-forming reactions, such as Suzuki coupling and olefin metathesis have been used with occasional success in dimerization and macrocyclization strategies.^{4,5} Herein we describe a new dimerization and macrocyclization strategy based on the Prins cyclization reaction.

The Prins cyclization is a powerful reaction that forms *cis*-2,6-disubstituted tetrahydropyrans (THPs) through the addition of an olefin to an oxocarbenium ion generated from the condensation of an aldehyde with a homoallylic alcohol.⁶ Recently, intramolecular Prins cyclizations have been utilized as key macrocyclization steps in the synthesis of several THP containing natural products (Figure 1 A).⁷ We report the extension of this methodology to the formation of oxacyclic macrodimers through sequential Prins dimerization and macrocyclization reactions (Figure 1 B). This synthetic strategy has been applied to a model for the marine macrodiolide clavosolide A.

srychnov@uci.edu.

Supporting Information Available Characterization data and experimental procedures for all compounds described are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The [n,n]-cyclophanes were chosen as targets for the initial study of this reaction, since the aromatic ring of these substrates provides rigidity that precludes the undesired macrocyclization reaction, and the starting materials were accessible from simple precursors. The Prins cyclization substrates **4**, **8**, and **12** were synthesized from the corresponding commercially available *para*-, *meta*-, or *ortho*-substituted ethyl iodobenzoate, respectively (Scheme 1). Palladium-mediated coupling of allyl alcohol and ethyl 4-iodobenzoate (**1**) yielded known aldehyde **2** in 85% yield.⁸ Nokami's menthone derived allyl-transfer reagent was utilized to yield optically pure *E*-homoallylic alcohol **3**.⁹ The ethyl ester was reduced with LiAlH₄ to provide the benzylic alcohol, which was selectively oxidized with MnO₂ to afford aldehyde **4** in 61% overall yield. The *meta*- and *ortho*-substituted substrates (**8** and **12**, respectively) were synthesized in a similar manner.

With appropriate starting materials in hand, the dimerization/macrocyclization reaction of aldehyde **4** was explored (Table 1). Previously, O₃ReOSiPh₃ has been shown to effectively catalyze Prins reactions of aromatic aldehydes.¹⁰ When aldehyde **4** was exposed to O₃ReOSiPh₃ at room temperature for 22 h, 33% of cyclophane **13** was isolated (Entry 1). The remainder of the mass was attributed to rhenium(VII) mediated polymerization. To diminish this byproduct, the reaction was run at lower concentration, which increased the yield of the dimer (Entry 2). Gratifyingly, decreasing the catalyst loading to 25% had little effect on the yield (Entry 3), but decreasing the loading further resulted in diminished yields (Entry 4). Other rhenium(VII) catalysts proved less effective than O₃ReOSiPh₃ (Entries 5 and 6). Heating the reaction in CH₂Cl₂ decreased the reaction time but had minimal effect on the overall yield (Entries 7 and 8). Finally, alternative Prins promoters were investigated. Both TESOTf¹¹ and trifluoroacetic acid¹² produced acylated variations of cyclophane **13** (Entries 9 and 10), but ultimately proved inferior to the rhenium(VII) conditions.

Having developed optimized conditions for the dimerization/macrocyclization reaction of the *para*-substituted aldehyde, the *ortho*- and *meta*-substituted aldehydes were employed to further expand the scope of the reaction (Scheme 2). The *ortho*-substituted aldehyde **12** afforded cyclized monomer **14** via an intramolecular Prins reaction in 90% yield. Prins macrocyclizations can be very effective, when not precluded by the geometry of the substrate.⁷ In contrast, when aldehyde **8** was exposed to the Prins conditions, dimeric cyclophane **15** was obtained in 28% yield. Surprisingly, the trimeric macrocycle **16** was also isolated in 13% yield. The remainder of the mass was associated with a small amount of starting material and a complex mixture of other products. The Prins reaction led to significant yields of dimer in two of the three cases examined, and in each case a single enantiomer and diastereomer of the product was obtained.

The C₂-symmetric macrodiolide (–)-clavosolide A, Figure 2, was isolated from the marine sponge *Myriastra clavosa* gathered off the coast of the Philippines.¹³ The unique architecture of this THP-containing macrodimer inspired several total syntheses¹⁴ and a structural revision.¹⁵ All reported approaches utilized Yamaguchi's macrolactonization conditions to form the dimer from a complex, THP containing monomer.¹⁶ The interesting architecture of clavosolide A appeared to be well suited to a Prins dimerization and macrocyclization strategy.

Due to concern over the lability of the cyclopropylcarbonyl moiety of clavosolide A,¹⁷ a model system was designed that replaced the problematic cyclopropyl side-chain with a cyclohexane ring. The cyclohexyl monomer was synthesized from two simple fragments **20** and **24** (Scheme 3 and 4). Enzymatic resolution of known β-lactone **17** with Lipase PS Amano in the presence of benzyl alcohol afforded the resolved (*S*)-lactone (**18**) and β-hydroxy ester **19**.¹⁸ Both substrates were then reduced with LiAlH₄, and the resultant enantiomeric diols were monoprotected as TBS-ethers **20** and **21**.

The synthesis of the acid fragment **24** began with DDQ-mediated deprotection of the *p*-methoxybenzyl ether of known silyl ether **22** to provide an inseparable mixture of alcohol **23** and *p*-anisaldehyde.¹⁹ The *p*-anisaldehyde was then removed by reduction and chromatography. Surprisingly, oxidation to the carboxylic acid proved challenging. Oxidation of alcohol **23** to the aldehyde followed by Lindgren–Pinnick oxidation afforded very poor yields of acid **24**. Additionally, TEMPO-mediated bleach oxidations²⁰ resulted in chlorination of the substrate. Instead, a large excess of pyridinium dichromate was employed over three days to produce acid **24** in 66% yield.²¹ The acid was then coupled to both alcohol enantiomers **20** and **21**, either through esterification to maintain the alcohol stereochemistry, or Mitsunobu reaction to invert the stereochemistry, to afford bis-TBS ether **25**.

With the completion of the monomer framework, a few simple manipulations were needed to test the key Prins dimerization/macrocyclization reaction (Scheme 5). Removal of the two silyl groups proved to be surprisingly difficult. Under standard deprotection conditions, only the primary silyl group was cleaved. Unfortunately, unmasking the primary alcohol under more forcing basic or acidic conditions led to a deleterious acyl migration. Ultimately, a large excess of HF-pyridine in THF was needed to avoid this side reaction, and the diol **26** (not shown) was formed in 88% yield. Finally, TEMPO-catalyzed selective oxidation successfully produced the requisite aldehyde **27**. Aldehyde **27** was labile and decomposed upon silica gel chromatography. Attempts to perform a Prins dimerization and macrocyclization reaction on the crude aldehyde under various conditions led to decomposition of the starting material, presumably through acid promoted elimination of the β -acyl aldehyde.

To circumvent this decomposition, aldehyde **27** was protected as dimethyl acetal **28**. This substrate proved much more manageable and was easily purified by column chromatography. It has been shown that Lewis acid-promoted Prins cyclizations of acetals are particularly effective with TESOTf in acetic acid.^{11,22} Gratifyingly, when acetal **28** was subjected to these conditions, dimeric macrolide **29** was produced in 43% yield. Using acetal **28** avoids the decomposition of the sensitive aldehyde **27**.

The first example of a Prins dimerization and macrocyclization reaction has been developed. This powerful methodology affords macrocyclic dimers while simultaneously enhancing molecular complexity. Several complex [n.n]-paraphanes were prepared in only five steps from commercially available material. A model for the synthesis of clavosolide A was successfully demonstrated, and studies will continue to apply this strategy to natural product synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

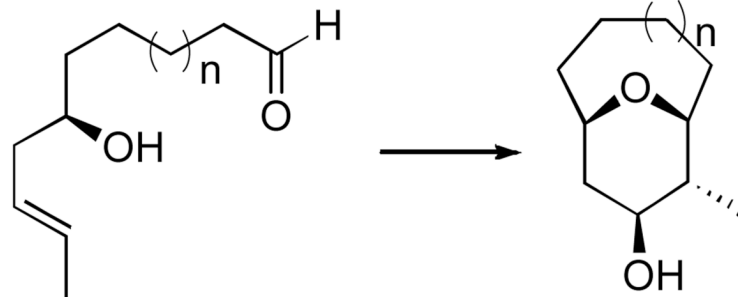
This work was supported by the National Institute of General Medicine (GM-43854) and by a generous gift from the Schering-Plough Research Institute. K.T. was supported by a fellowship from the Royal Thai Government and M.R.G. was supported by a Lilly Graduate Research Fellowship.

References

1. Norcross RD, Paterson I. *Chem. Rev* 1995;95:2041–2114.
2. Kang EJ, Lee E. *Chem. Rev* 2005;105:4348–4378. [PubMed: 16351047]
3. (a) Wakamatsu T, Yamada S, Ban Y. *Heterocycles* 1986;24:309–312. (b) Furstner A, Mlynarski J, Albert M. J. *Am. Chem. Soc* 2002;124:10274–10275. [PubMed: 12197718] (c) Panek JS, Porco JA Jr, Lobkovsky E, Beeler AB. *Org. Lett* 2003;12:2149–2152. [PubMed: 12790551] (d) Barth R, Mulzer J. *Angew. Chem., Int. Ed* 2007;46:5791–5794.

4. (a) Cheung LL, Marumoto S, Anderson CD, Rychnovsky SD. *Org. Lett* 2008;10:3101–3104. [PubMed: 18543942] (b) Nicolaou KC, Nold AL, Milburn RR, Schindler CS. *Angew. Chem., Int. Ed* 2006;45:6527–6532.
5. (a) HWE olefinations: Hoye TR, Humpal PE, Moon B. *J. Am. Chem. Soc* 2000;122:4982–4983. (b) Olefin metathesis: Smith AB III, Adams CM, Kozmin SA, Paone DV. *J. Am. Chem. Soc* 2001;123:5925–5937. [PubMed: 11414825] (c) Condensations: Hoye TR, Ye Z, Yao LJ, North JT. *J. Am. Chem. Soc* 1996;118:12074–12081.
6. Recent reviews on the Prins cyclization: (a) Pastor IM, Yus M. *Curr. Org. Chem* 2007;11:925–957. (b) Snider, BB. *Comprehensive Organic Synthesis*. Trost, BM.; Fleming, I.; Heathcock, CH., editors. Vol. Vol. 2. New York: Pergamon Press; 1991. p. 527-561. (c) Adams DR, Bhatnagar SP. *Synthesis* 1977:661–672. (d) Overman LE, Pennington LD. *J. Org. Chem* 2003;68:7143–7157. [PubMed: 12968864]
7. (a) Custar DW, Zabawa TP, Scheidt KA. *J. Am. Chem. Soc* 2008;130:804–805. [PubMed: 18161979] (b) Woo SK, Kwon MS, Lee E. *Angew. Chem., Int. Ed* 2008:3242–3244. (c) Wender PA, DeChristopher BA, Schrier AJ. *J. Am. Chem. Soc* 2008;130:6658–6659. [PubMed: 18452292] (d) Bahnc KB, Rychnovsky SD. *J. Am. Chem. Soc* 2008;130:13177–13181. [PubMed: 18767844]
8. (a) Taylor EC, Gillespie P, Patel M. *J. Org. Chem* 1992;57:3218–3225. (b) Watson SE, Taylor EC, Patel H. *Synth. Commun* 1998;28:1897–1905.
9. (a) Nokami J, Nomiya K, Matsuda S, Imai N, Kataoka K. *Angew. Chem., Int. Ed* 2003;42:1273–1276. (b) Nokami J, Ohga M, Nakamoto H, Matsubara T, Hussain H, Kataoka K. *J. Am. Chem. Soc* 2001;123:9168–9169. [PubMed: 11552828]
10. Tadpetch K, Rychnovsky SD. *Org. Lett* 2008;10:4839–4842. [PubMed: 18816133]
11. Ko HM, Lee DG, Kim MA, Kim HJ, Park J, Lah MS, Lee E. *Tetrahedron* 2007;63:5797–5805.
12. Barry CSJ, Crosby SR, Harding JR, Hughes RA, King CD, Parker GD, Willis CL. *Org. Lett* 2003;5:2429–2432. [PubMed: 12841747]
13. (a) Erickson KL, Gustafson KR, Pannell LK, Beutler JA, Boyd MR. *J. Nat. Prod* 2002;65:1303–1306. [PubMed: 12350152] (b) Rao MR, Faulkner DJ. *J. Nat. Prod* 2002;65:386–388. [PubMed: 11908986]
14. (a) Carrick JD, Jennings MP. *Org. Lett* 2009;11:769–772. [PubMed: 19125666] (b) Chakraborty TK, Reddy VR, Chattopadhyay AK. *Tetrahedron Lett* 2006;47:7435–7438. (c) Barry CS, Elsworth JD, Seden PT, Bushby N, Harding JR, Alder RW, Willis CL. *Org. Lett* 2006;8:3319–3322. [PubMed: 16836395] (d) Smith AB III, Simov V. *Org. Lett* 2006;8:3315–3318. [PubMed: 16836394] (e) Son JB, Kim SN, Kim NY, Lee DH. *Org. Lett* 2006;8:661–664. [PubMed: 16468736]
15. (a) Chakraborty TK, Reddy VR. *Tetrahedron Lett* 2006;47:2099–2102. (b) Barry CS, Bushby N, Charmant JPH, Elsworth JD, Harding JR, Willis CL. *Chem. Commun* 2005:5097–5099.
16. Yamaguchi MA, Katsuki T, Sacki H, Hirata K, Inanaga J. *Bull. Chem. Soc. Jpn* 1979;52:1989–1993.
17. Poulter DC, Winstein SJ. *J. Am. Chem. Soc* 1969;91:3650–3652.
18. (a) Nelson SG, Spencer KL. *J. Org. Chem* 2000;65:1227–1230. [PubMed: 10814079] (b) Nelson SG, Wan Z, Peelen TJ, Spencer KL. *Tetrahedron Lett* 1999:6535–6539.
19. Eggen M, Mossman CJ, Buck SB, Nair SK, Bhat L, Ali SM, Reiff EA, Boge TC, Georg GI. *J. Org. Chem* 2000;65:7792–7799. [PubMed: 11073583]
20. Zhao MM, Li J, Mano E, Song ZJ, Tschaen DM. *Org. Synth* 2005;81:195–203.
21. Corey EJ, Schmidt G. *Tetrahedron Lett* 1979;20:399–402.
22. (a) Fujioka H, Okitsu T, Sawama Y, Murata N, Li R, Kita Y. *J. Am. Chem. Soc* 2006;128:5930–5938. [PubMed: 16637661] (b) Tsunoda T, Suzuki M, Noyori R. *Tetrahedron Lett* 1980;21:71–74.

A. Prins macrocyclization



B. Prins dimerization/macrocyzation

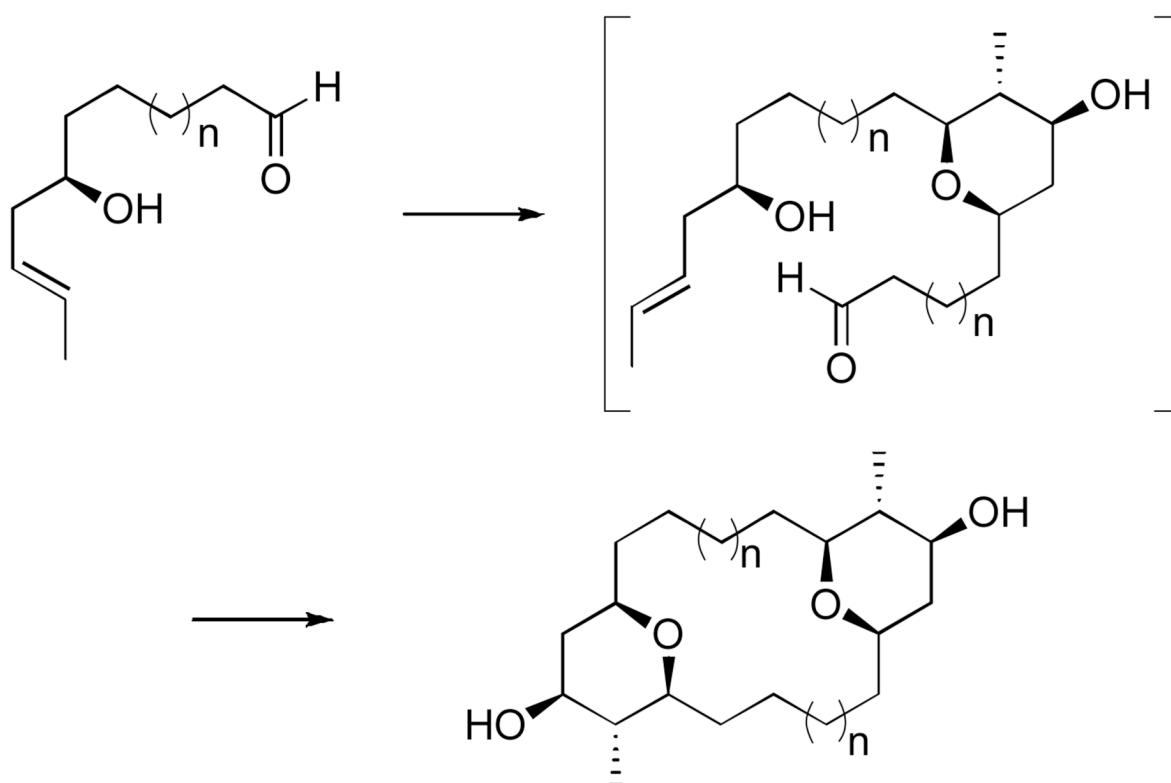


Figure 1.
Comparison of Prins macrocyclization reactions.

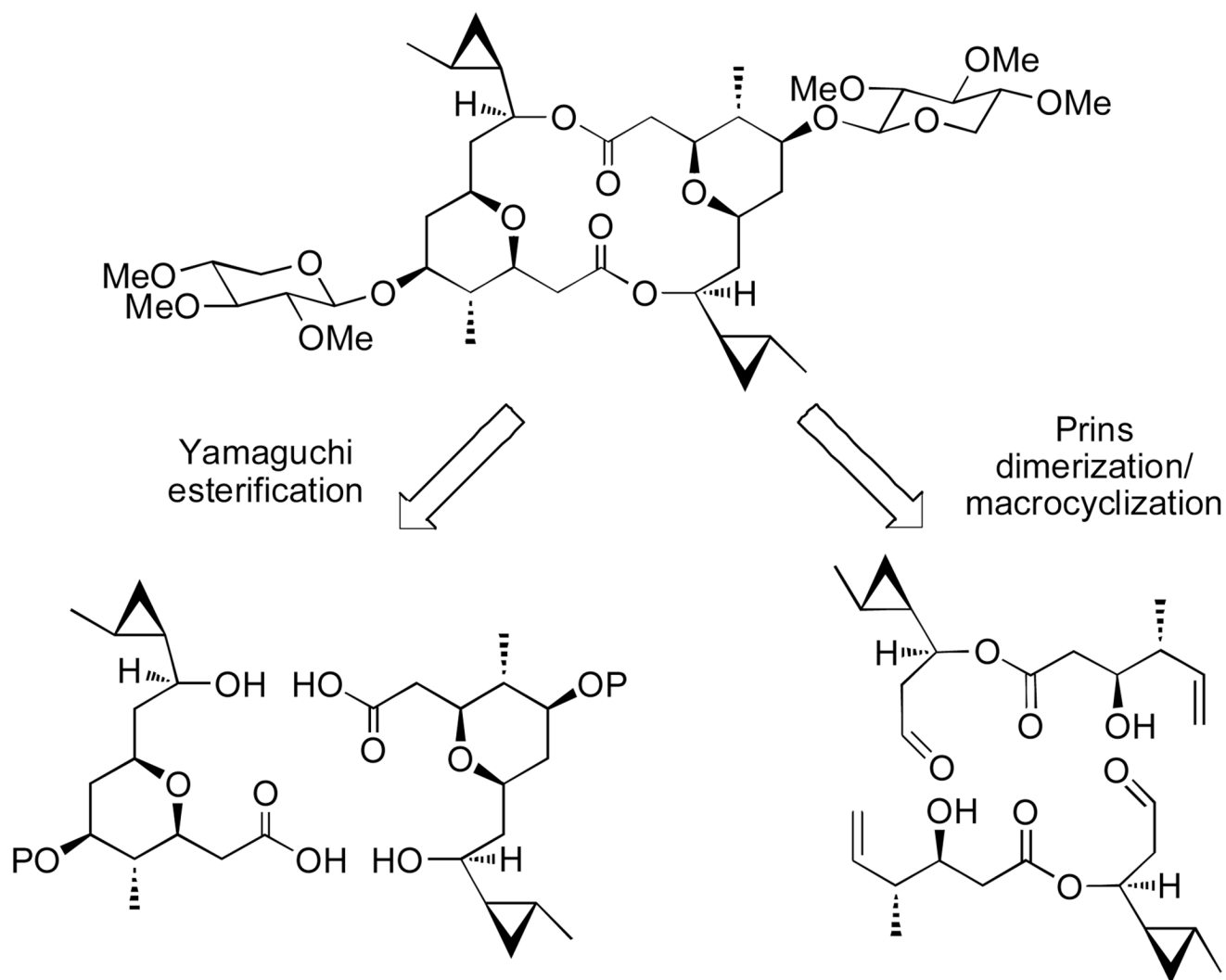
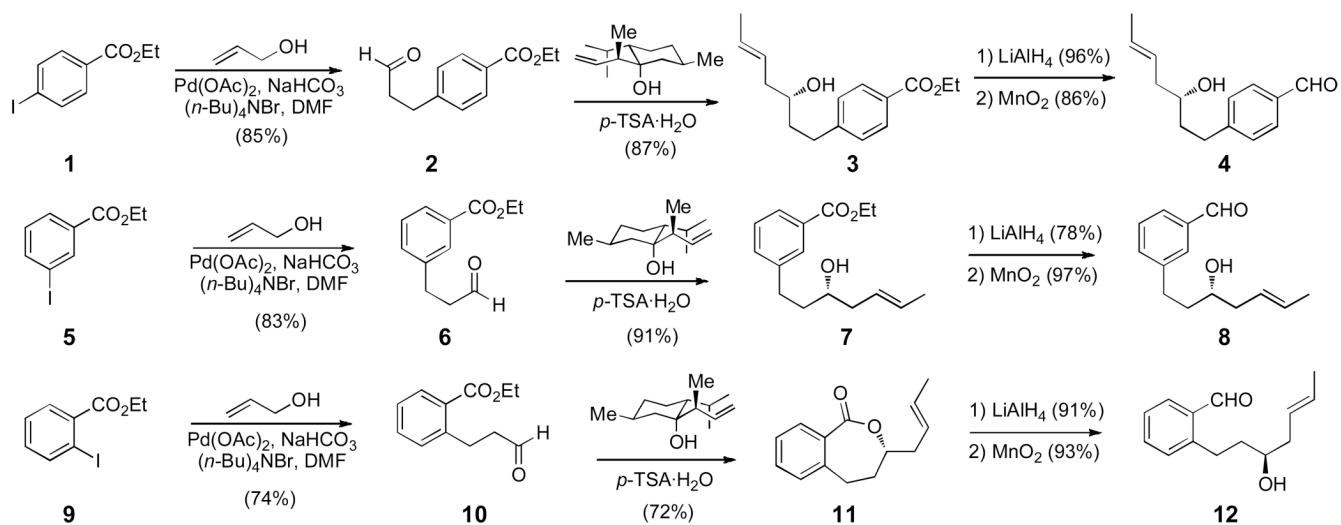
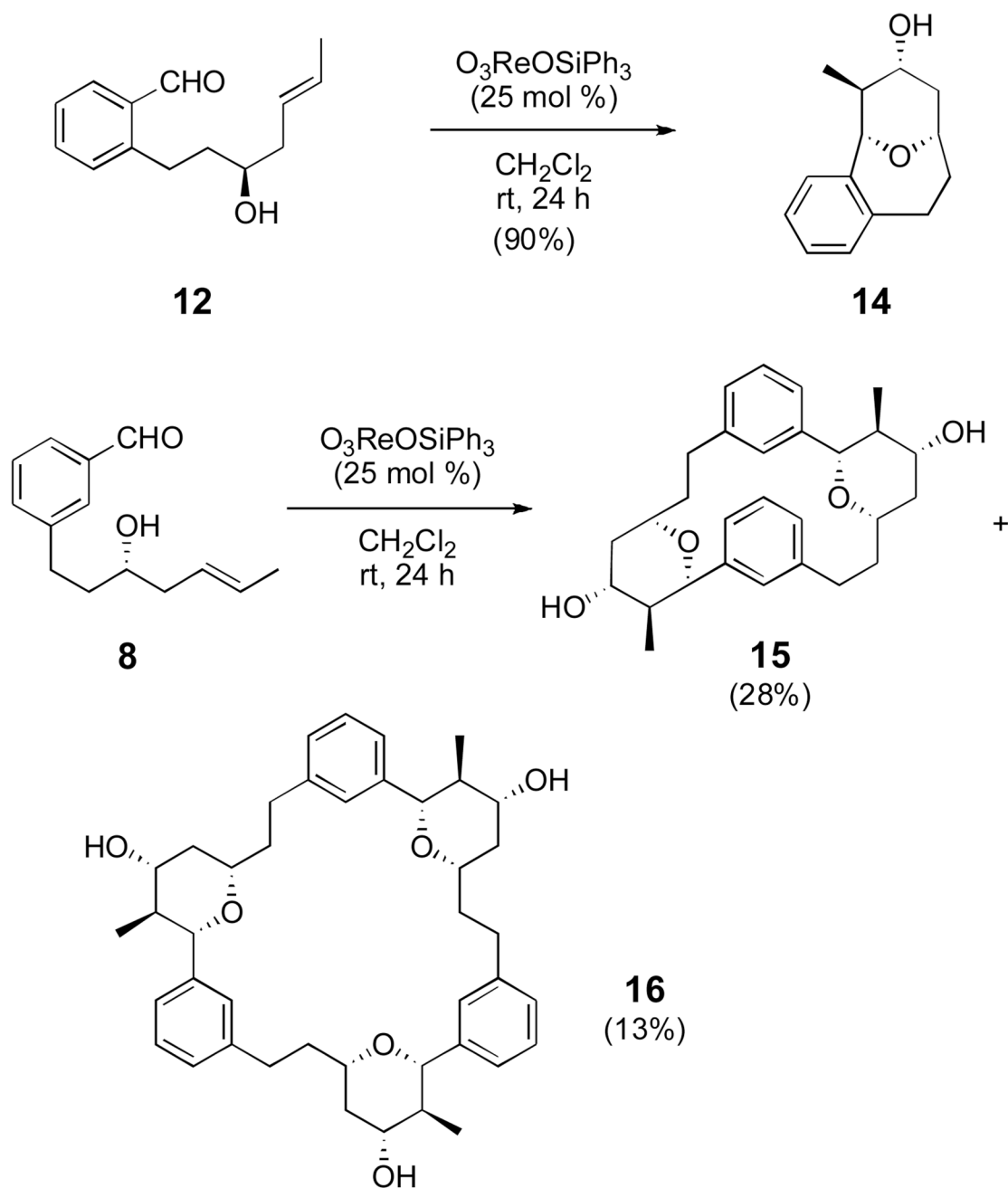


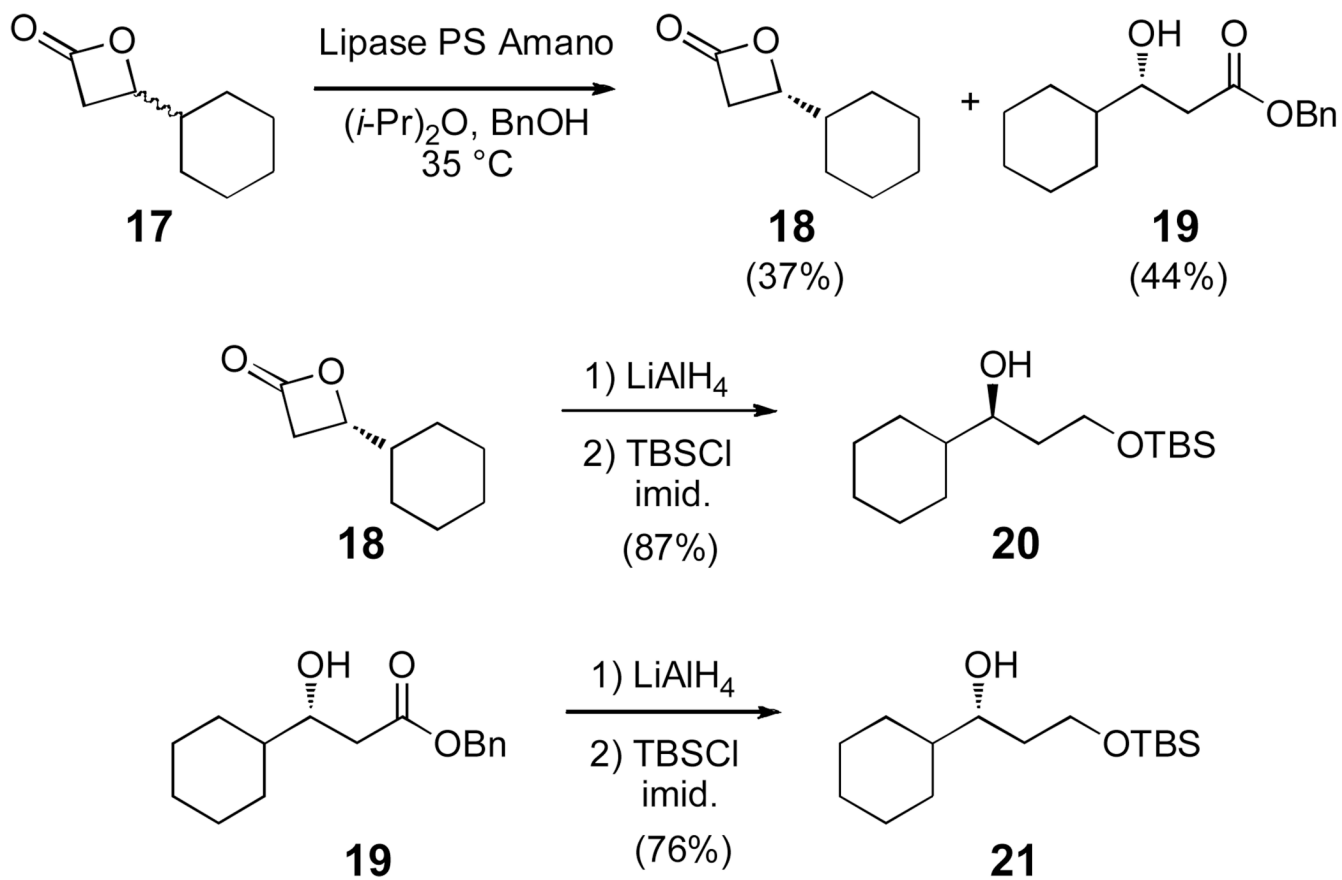
Figure 2.
Two alternative strategies for the dimerization and cyclization of (-)-clavosolide A



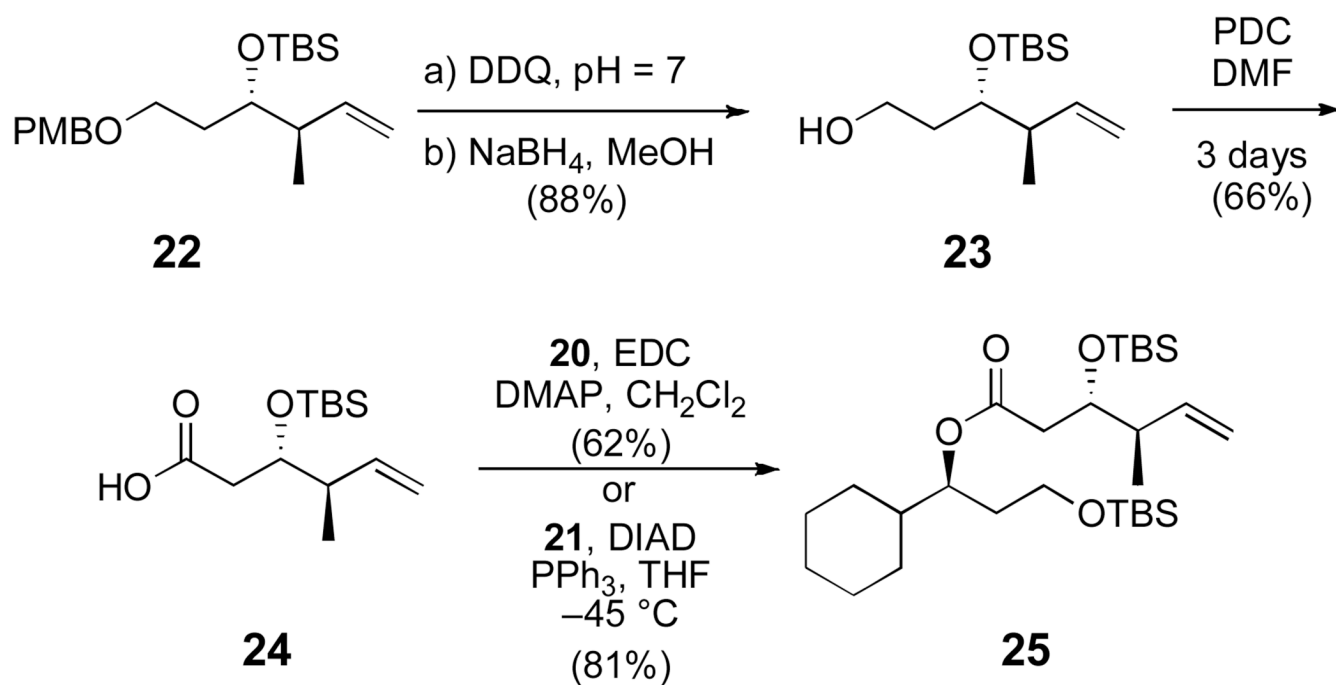
Scheme 1.
Synthesis of the Aldehyde Monomers



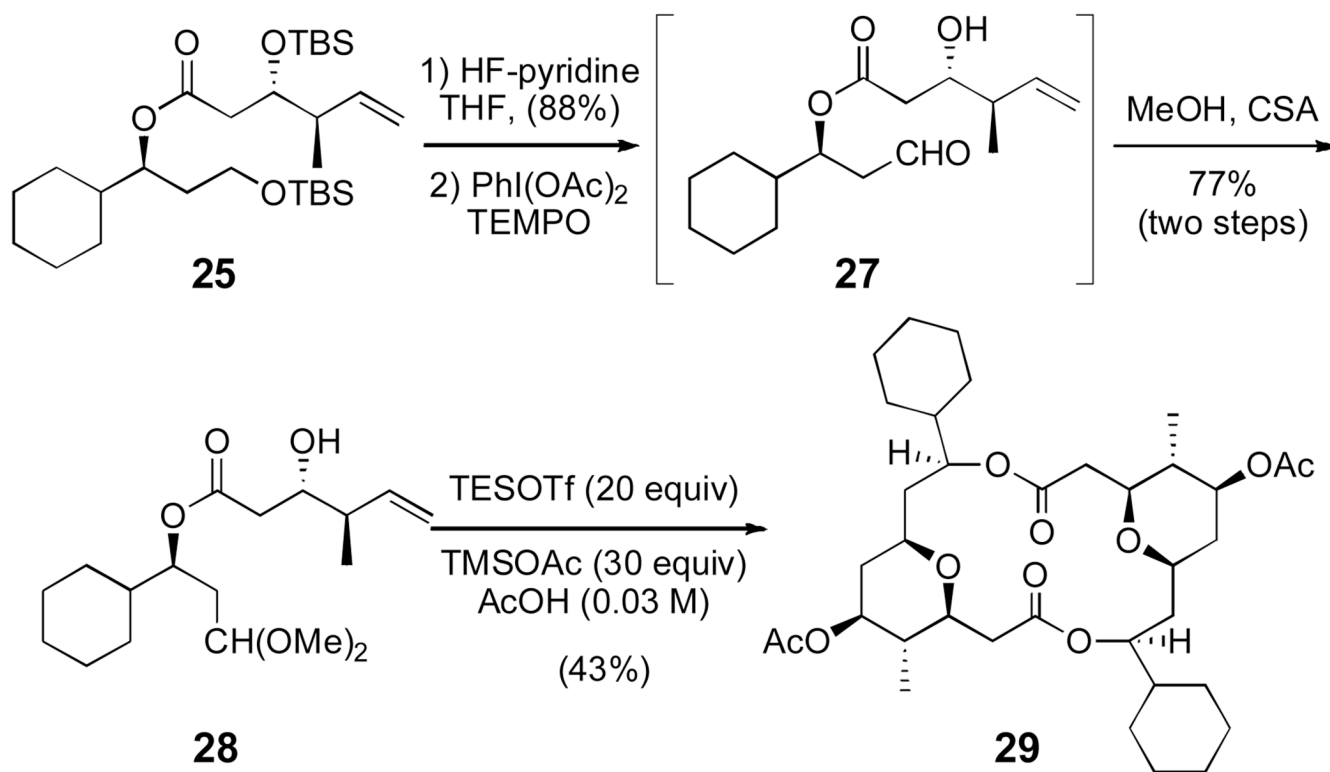
Scheme 2.
Optimized Prins Macrocyclization/Dimerization Reactions



Scheme 3.
Synthesis of the cyclohexyl alcohols **20** and **21**



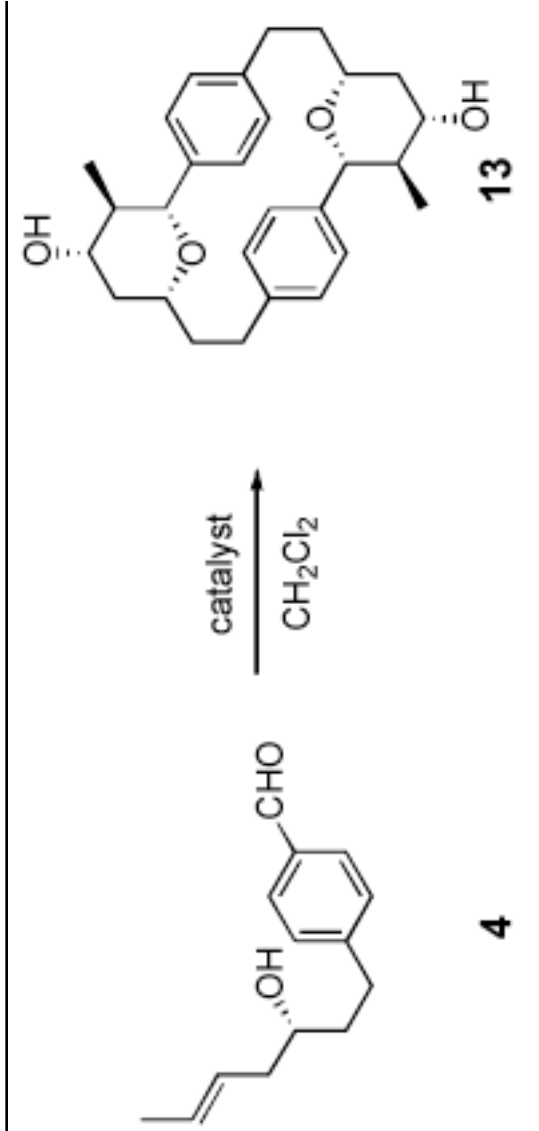
Scheme 4.
Synthesis of the ester monomer **25**



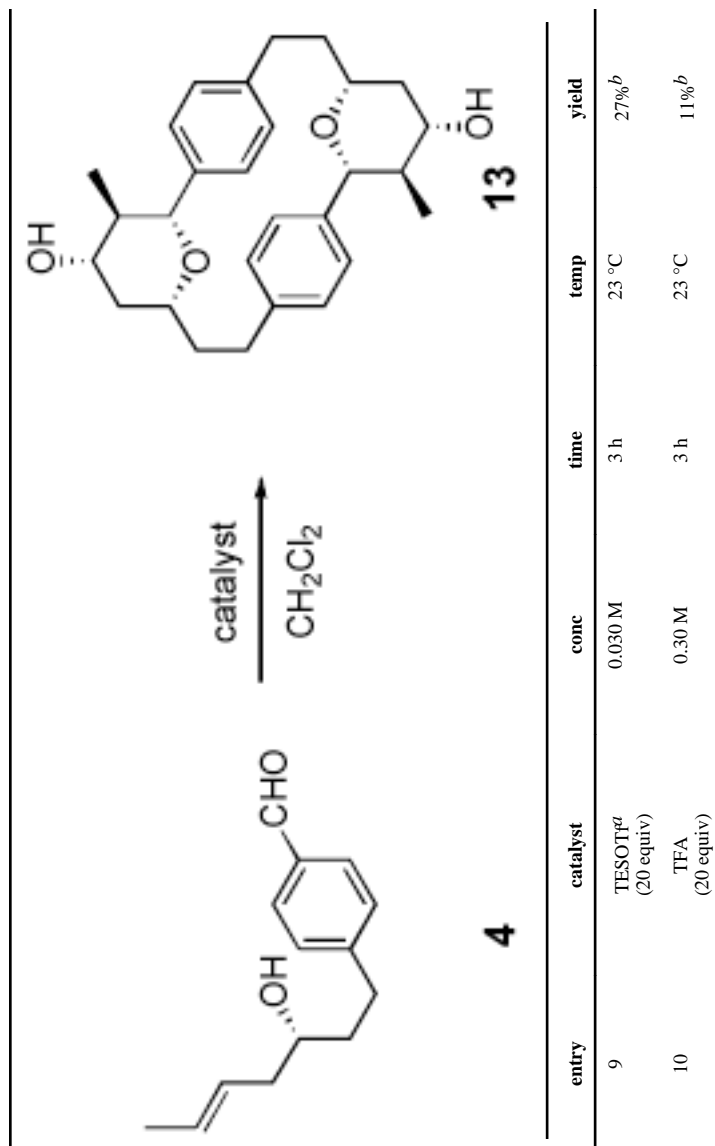
Scheme 5.
Prins dimerization and macrocyclization

Table 1

Screening Prins Dimerization/Macrocyclization Conditions



entry	catalyst	conc	time	temp	yield
1	O ₃ ReOSiPh ₃ (40 mol %)	0.10 M	22 h	23 °C	33%
2	O ₃ ReOSiPh ₃ (50 mol %)	0.050 M	24 h	23 °C	53%
3	O₃ReOSiPh₃ (25 mol %)	0.050 M	24 h	23 °C	51%
4	O ₃ ReOSiPh ₃ (5 mol %)	0.050 M	24 h	23 °C	26%
5	aq O ₃ ReOH (50 mol %)	0.050 M	24 h	23 °C	29%
6	Re ₂ O ₇ (50 mol %)	0.045 M	25 h	23 °C	38%
7	O ₃ ReOSiPh ₃ (25 mol %)	0.050 M	5 h	40 °C	51%
8	O ₃ ReOSiPh ₃ (5 mol %)	0.050 M	5 h	40 °C	42%



^aRun in AcOH with 30 equiv TMSOAc.

^bYield after hydrolysis of the crude acyl trapped product by MeOH/K₂CO₃.