Dual Macrolactonization/Pyran-Hemiketal Formation via Acylketenes: Applications to the Synthesis of (−)-Callipeltoside A and a Lyngbyaloside B Model System

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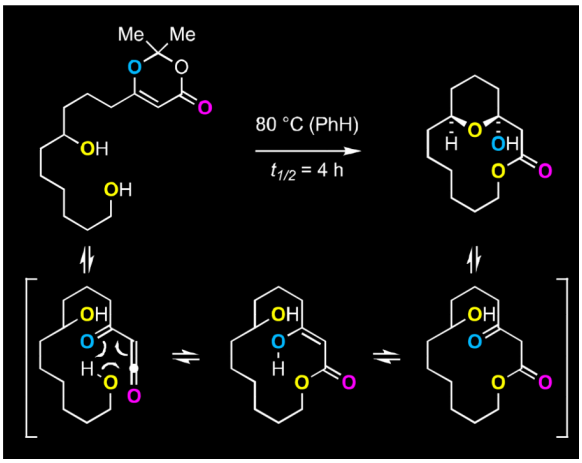
Dual Macrolactonization/Pyran-Hemiketal Formation via Acylketenes [and its Application to Syntheses of (−)-Callipeltoside A and a Lyngbyaloside B Model System]

Thomas R. Hoye, **Michael E. Danielson**, **Aaron E. May**, and **Hongyu Zhao**
Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455 (USA)

Thomas R. Hoye: hoye@umn.edu

Abstract



Thermal generation of acylketenes in diol-containing substrates results in dual macrocyclization/pyran-hemiketal formation. This transformation expands the scope of acylketene macrolactonizations and their application to the synthesis of complex macrolides. Triol and even tetrol substrates also have been closed in highly regioselective fashion. Additionally, the challenging macrolactonization of a tertiary alcohol was achieved.

Keywords

acylketenes; regioselective macrolactonization; concerted addition

Acylketenes (**2**) are often employed as electrophiles to trap alcohols to construct β-ketoesters **4** via concerted addition[i] of the hydroxylic nucleophile to produce the transient enol **3** (Scheme 1).[ii] Thermolysis of 1,3-dioxin-4-one derivatives **1** is the most common method used for generation of **2**.[iii] Boeckman pioneered the application of these reactive species in the context of complex molecule synthesis.[iv] Namely, macrocyclic lactones (and lactams) can be constructed by intramolecular reactions of hydroxy-(or amino-)containing acylketenes.[v]

Correspondence to: Thomas R. Hoye, hoye@umn.edu.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

As part of our research program directed toward the synthesis of complex pyran-containing macrolides (*cf.*, **5** and **6**, Figure 1), we have expanded the scope of this powerful transformation[vi] by exploring the use of substrates containing multiple hydroxyl groups.[vii] The mechanism of addition of hydroxylic nucleophiles to acylketene allows for this process to be highly regioselective, as reported here for substrates containing up to four free hydroxyl groups. As we report here, this reagent- and catalyst-free transformation allows for rapid, direct, and selective construction of the macrolactone/pyran-hemiketal substructure units present in callipeltoside A (**5**)[viii] and lyngbyaloside B (**6**).[ix]

We chose the prototypical substrate **7**[x] for use in testing the concept of dual macrolactonization/pyran-hemiketal formation (Scheme 2). When this diol was heated in benzene at 80 °C the macrolactone/pyran **8** was cleanly formed (as an *ca.* 9:1 ratio of **8** to its C3-anomer) in 80% isolated yield.

While we do not know the exact sequence of events leading to **8**, if the distal C13-hydroxyl group in acylketene **9** were to add in a concerted 1,4-addition,[i] the enol-lactone **10** would be formed. Rapid tautomerization followed by hemiketal formation within ketone **11** would account for formation of **8**. Alternative intermediates or processes can be envisioned for this transformation of **7** to **8**. *i*) Hemiketal formation in **9** prior to lactonization would give **12**, which could further cyclize to the macrolactone/pyran **8**. We presume that the acylketene **9** would lactonize considerably faster than the simple ketene **12** [*e.g.,* water reacts with acetylketene (AcCH=C=O) ~42,000 times faster than with ketene (H_2C=C=O) itself].[xi] Moreover, there are no intermediates involved in the **9** to **10** transformation, but hemiketal formation (**9** to **12**) likely requires catalysis by an external agent. Thus, we are inclined to think that **12** is not involved in the process. *ii*) Conjugate addition of the secondary carbinol to the enoate moiety in **10** could give rise directly to **8**. *iii*) Trapping of the ketene by the secondary C7-OH in **9** would give the eight-membered lactone **13**.[xii] None was observed, but the further conversion of **13** into **8** by translactonization cannot be ruled out. *iv*) Adventitious water could trap either of the ketenes **9** or **12** to give the β-ketoacid **14**, which would be expected to decarboxylate to the methyl ketone **15**. When no special care was taken to predry the benzene solvent, none of the methyl ketone **15** was observed. Even when excess water (0.5 M; biphasic) was added at the outset to a benzene solution of **7** (0.0003 M) that was then refluxed, lactone **8** was still the predominant product, but methyl ketone **15** was also observed (*ca.* 2:1 by ^{1}H NMR analysis). When purified **8** was heated for 12 h in a benzene solution to which excess water had been added, no reaction was observed; in particular, none of **15** was formed. When this experiment was repeated using D_2O, partial (mono- and di-) deuteration of C2 in **8** occurred.

Taken collectively, the observations under *iv*) above are consistent with reversion of lactone **8** to the keto/enol pair **11** and **10**, but not of **10** back to the acylketene **9**. On the other hand, the observed $t_{1/2}$ for the reaction and formation of methyl ketone **15** are consistent with an initial, rate-limiting thermolysis of dioxinone **7** to form the acylketene **9**.[xiii] It is interesting to consider the fact that **8** was formed in preponderance to **15** even when the benzene reaction medium was saturated with water. Since addition of a hydroxylic nucleophile to an acylketene is a concerted event,[i] the relative O–H bond strengths of water (119 kcal mol^{-1}) vs. alcohols (104–107 kcal mol^{-1}) are important.[xiv] We suggest that partial cleavage of the O–H bond, uniquely strong in water, renders hydrolysis considerably slower, vis-à-vis alcoholysis. That is, lactonization within **9** is favored over its competitive hydrolysis. We can further suggest that this is likely why acylketene macrolactonization reactions have proven to be so successful in the service of late stage (and often small-scale) construction of complex molecules.[vi]

We have used the title dual cyclization process to achieve a chemical synthesis of callipeltoside A (**5**),[xv] a natural product that was first synthesized via a key acylketene cyclization to a late stage β-ketomacrolactone intermediate.[xvi] Our key experiments are shown in Scheme 3. In the 7, 13-diol **16**[xvii] two of the four hydroxyl groups are free and two are capped as silyl ethers. Likewise, the C13-epimeric diol bis-silylether **20** was studied. Each of these dioxinone derivatives smoothly cyclized to the hemiketals **17** and **21** (in 76 and 86% yields, respectively) when refluxed in benzene solution for 12 hours. We next examined the 5,7,13-triol substrate **22**, in which the C5-hydroxyl group was now exposed. This substrate also cyclized in good yield to the lactone **23**, and the six-membered pyranone ring that would have arisen by acylation of the C5-OH by the ketene was not observed;[xviii] that is, the C5-hydroxyl was a bystander. To test whether pyrone formation was even feasible, the thermolysis of the C5-*mono*-alcohol **24** was examined. The pyrone **25** was isolated in 54% yield, establishing that the C5-hydroxyl group is capable of trapping the acylketene if there are not remote hydroxyl groups more geometrically suited to outcompete the (likely non-concerted) trapping by the C5-OH.

Finally, the fully deprotected 5,7,13,14-tetrol substrate **18** was studied. Remarkably, this substrate, *having four free hydroxyl groups*, each, in principle, capable of participating in lactonization, closed to give the macrolactone **19** as the major product in 53% yield; no other constitutional isomer was identified. Most interesting of all, perhaps, is the selective reaction of the secondary C13-hydroxyl rather than its vicinal, primary C14-hydroxyl group. To benchmark the inherent reactivity difference within a terminal vicinal diol, we reacted an excess of 1,2-butanediol with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one in refluxing benzene or toluene and observed a 3:1 preference for formation of the primary β-ketoester. This result suggests that the regioselectivity of lactonization to the secondary C13-OH in **18** is conformational in origin, rather than a function of a more inherent property (preferential hydrogen bonding/nucleophilicity) of a 1,2-diol moiety.

Lyngbyaloside B (**6**) contains both a pyran hemiketal and a tertiary macrolactone subunit, the latter an uncommon structural element in natural products. Since macrolactonization reactions involving the OH group of a tertiary alcohol are also quite rare,[xix] we wondered if such an approach to the synthesis of **6** was feasible. More specifically, could the dual macrolactonization/pyran formation create a tertiary macrolactone? To test that question, we prepared the model substrates **26β** and **26α** (each as an essentially 1:1 mixture of C11-epimers).[x] In each of these C7/C13-diols, if the tertiary C13-OH trapped the acylketene too slowly, competing 8-membered lactone formation[xii] was seen as a potential complication. Finally, it was also not clear whether the macrolactone product would be stable over the course of the reaction, since *t*-butylacetoacetate thermally extrudes *t*-butanol at essentially the same rate as acetone extrusion from dioxinones.[xx]

In the event, we were very pleased to observe that heating **26β** or **26α** cleanly produced the lactone/pyran **27β** or **27α**, respectively, as the only isolable product. To our knowledge, this is the most efficient macrolactonization involving a tertiary carbinol center, a fact that further demonstrates the power of acylketene methodology. Again, heating to reflux a toluene solution of **27β** that had been doped with excess water for 40 min (*ca.* two half-lives for acylketene formation from either dioxinones or *t*-alkyl acetoacetates)[xx] resulted in no observable decomposition of **27β**. It is likely that the internal trapping of the β-ketolactone as its hemiketal, thereby minimizing cycloreversion to regenerate the reactive acylketene intermediate, contributes to the success of these transformations.

In conclusion, we have developed a process for dual macrolactonization/pyran-hemiketal formation via the trapping of thermally generated acylketenes by various diol substrates. These results expand the scope of acylketene macrocyclizations. We have further exploited

the concerted nature of the mechanism of the key cyclization event to lactonize regioselectively triol and tetrol substrates (**22** and **18**, respectively). Additionally, the challenging macrolactonization of the tertiary alcohols **26** was achieved, which is encouraging in the context of ongoing lyngbyaloside B synthesis studies. More broadly, the dual cyclization transformation described here adds dimensionality to the Boeckman cyclization, particularly in the context of complex molecule synthesis.

Experimental Section

Representative example: Synthesis of macrolactone/pyran 21

Benzene (200 mL) was placed in a round bottom flask equipped with a Dean Stark trap, brought to reflux until 20 mL was removed via the trap, and cooled to room temperature. The trap was removed and diol **20** (18 mg, 0.030 mmol) in benzene (2 mL) was transferred into the flask with a pipette. A reflux condenser was attached to the flask and the mixture was refluxed for 12 hours. The flask was then cooled to room temperature, solvent was removed under reduced pressure, and the residue was purified by flash chromatography (10% EtOAc in hexanes) to afford macrolactone **21** (14 mg, 86%).

See Supporting Information for characterization data for compounds **7**, **8**, **17**, **19**, **21**, **23**, **25**, **26β**, **26α**, **27β**, and **27α**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

i. a) Freiermuth B, Wentrup C. J. Org. Chem. 1991; 56:2286–2289.b) Birney DM, Wagenseller PE. J. Am. Chem. Soc. 1994; 116:6262–6270.

ii. For a review on the preparation and use of acylketenes, see: Wentrup C, Heilmayer W, Kollenz G. Synthesis. 1994:1219–1248.

iii. Clemens RJ, Hyatt JA. J. Org. Chem. 1985; 50:2431–2435.

iv. a) Boeckman RK Jr, Perni RB. J. Org. Chem. 1986; 51:5486–5489.b) Boeckman RK Jr, Pruitt JR. J. Am. Chem. Soc. 1989; 111:8286–8288.

v. a) Boeckman RK Jr, Weidner CH, Perni RB, Napier JJ. J. Am. Chem. Soc. 1989; 111:8036–8037.b) Paquette LA, Macdonald D, Anderson LG, Wright J. J. Am. Chem. Soc. 1989; 111:8037–8039.

vi. For a review of the use of macrolactonizations in natural product synthesis, see: Parenty A, Moreau X, Campagne J-M. Chem. Rev. 2006; 106:911–939. [PubMed: 16522013]

vii. The only example we have located of an acyclketene lactonization of a substrate containing more than one hydroxyl group is that of a 2°/3° diol substrate used in a synthesis of (−)-kromycin and reported in ref 4b. Also, such a process might have been operative in the key lactonization used in a synthesis of (+)-acutiphycin: Moslin RM, Jamison TF. J. Org. Chem. 2007; 72:9736–9745. [PubMed: 17985925] Examples of diol lactonizations via other methods can be found in ref vi.

viii. a) Zampella A, D'Auria MV, Minale L, Debitus C, Roussakis CJ. J. Am. Chem. Soc. 1996; 118:11085–11088.b) Zampella A, D'Auria MV, Minale L. Tetrahedron. 1997; 53:3243–3248.

ix. Luesch H, Yoshida WY, Harrigan GG, Doom JP, Moore RE, Paul VJ. J. Nat. Prod. 2002; 65:1945–1948. [PubMed: 12502348] For structurally related lyngbouilloside, see: Tan LT, Marquez BL, Gerwick WH. J. Nat. Prod. 2002; 65:925–928. [PubMed: 12088441]

x. For the preparation of this substrate, see Supporting Information.

xi. Chiang Y, Guo HX, Kresge AJ, Tee OS. J. Am. Chem. Soc. 1996; 118:3386–3391.

xii. Petasis NA, Patane MA. J. Chem. Soc., Chem. Commun. 1990:836–837.

xiii. Clemens RJ, Witzeman JS. J. Am. Chem. Soc. 1989; 111:2186–2193.

xiv. For a critical analysis and compilation of bond dissociation energies see: Blanksby SJ, Ellison GB. Acc. Chem. Res. 2003; 36:255–263. [PubMed: 12693923]

xv. a) Zhao, H. Ph. D. Thesis. University of Minnesota; 2000. b) Danielson, ME. Ph. D. Thesis. University of Minnesota; 2003.

xvi. Trost BM, Gunzner JL. J. Am. Chem. Soc. 2001; 123:9449–9450. [PubMed: 11562231] Trost BM, Dirat O, Gunzner JL. Angew. Chem. Int. Ed. 2002; 41:841–843. Trost BM, Gunzner JL, Dirat O, Rhee YH. J. Am. Chem. Soc. 2002; 124:10396–10415. [PubMed: 12197742] For a listing of all reports of total syntheses of callipeltoside A see: Evans DA, Burch JD, Hu E, Jaeschke G. Tetrahedron. 2008; 64:4671–4699.

xvii. For preparation of compounds **16**, **18**, **20**, **22**, and **24** see ref xvb.

xviii. Sato M, Sakaki J, Sugita Y, Yasuda S, Sakoda N, Kaneko C. Tetrahedron. 1991; 47:5689–5708.

xix. a) Masamune S, Hayase Y, Schilling W, Chan W, Bates GS. J. Am. Chem. Soc. 1977; 99:6756–6758. [PubMed: 893906] b) Booth PM, Fox CM, Ley SV. J. Chem. Soc. Perkin Trans. I. 1987:121–129.c) Clyne DS, Weiler L. Tetrahedron. 1999; 55:13659–13682.

xx. Witzeman JS, Nottingham WD. J. Org. Chem. 1991; 56:1713–1718.

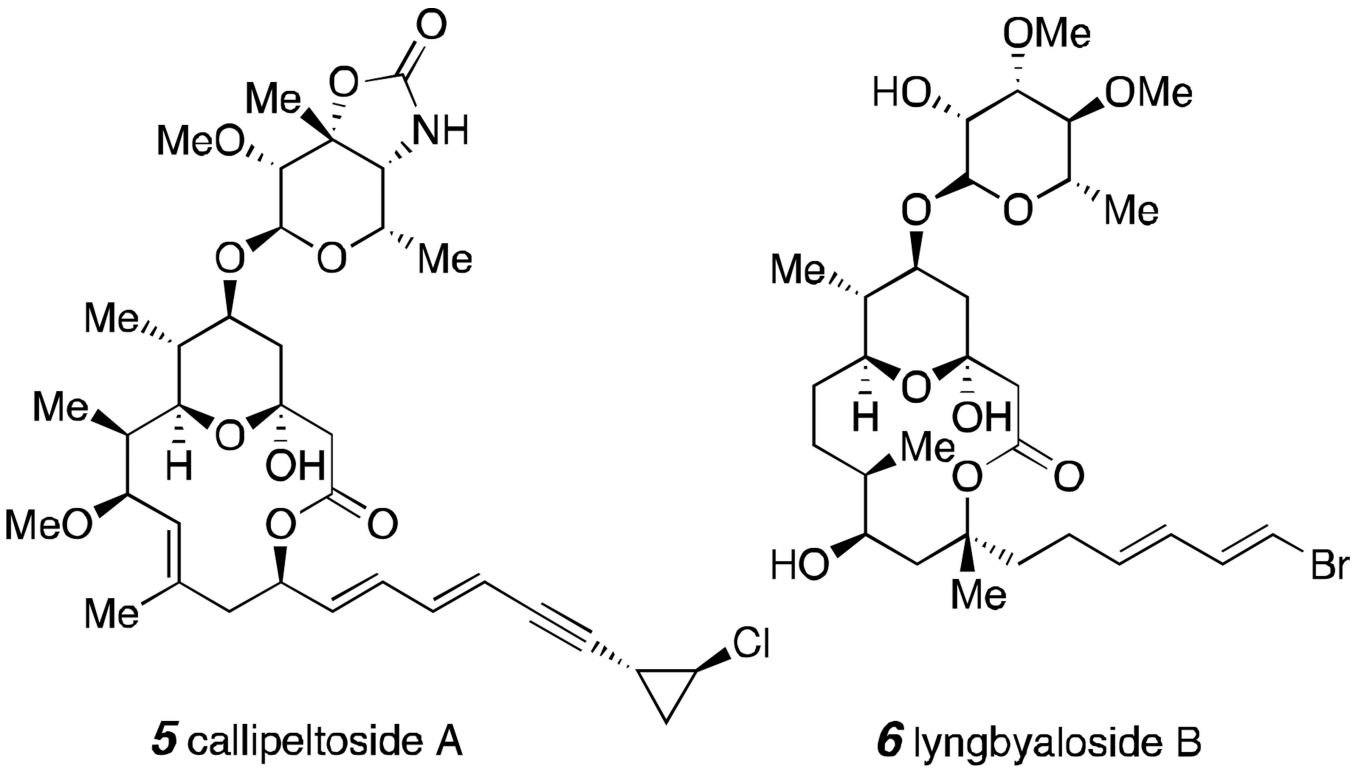
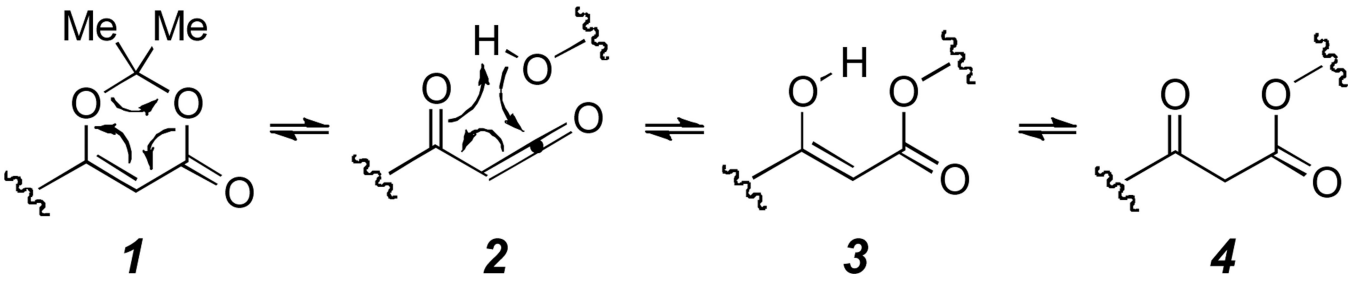
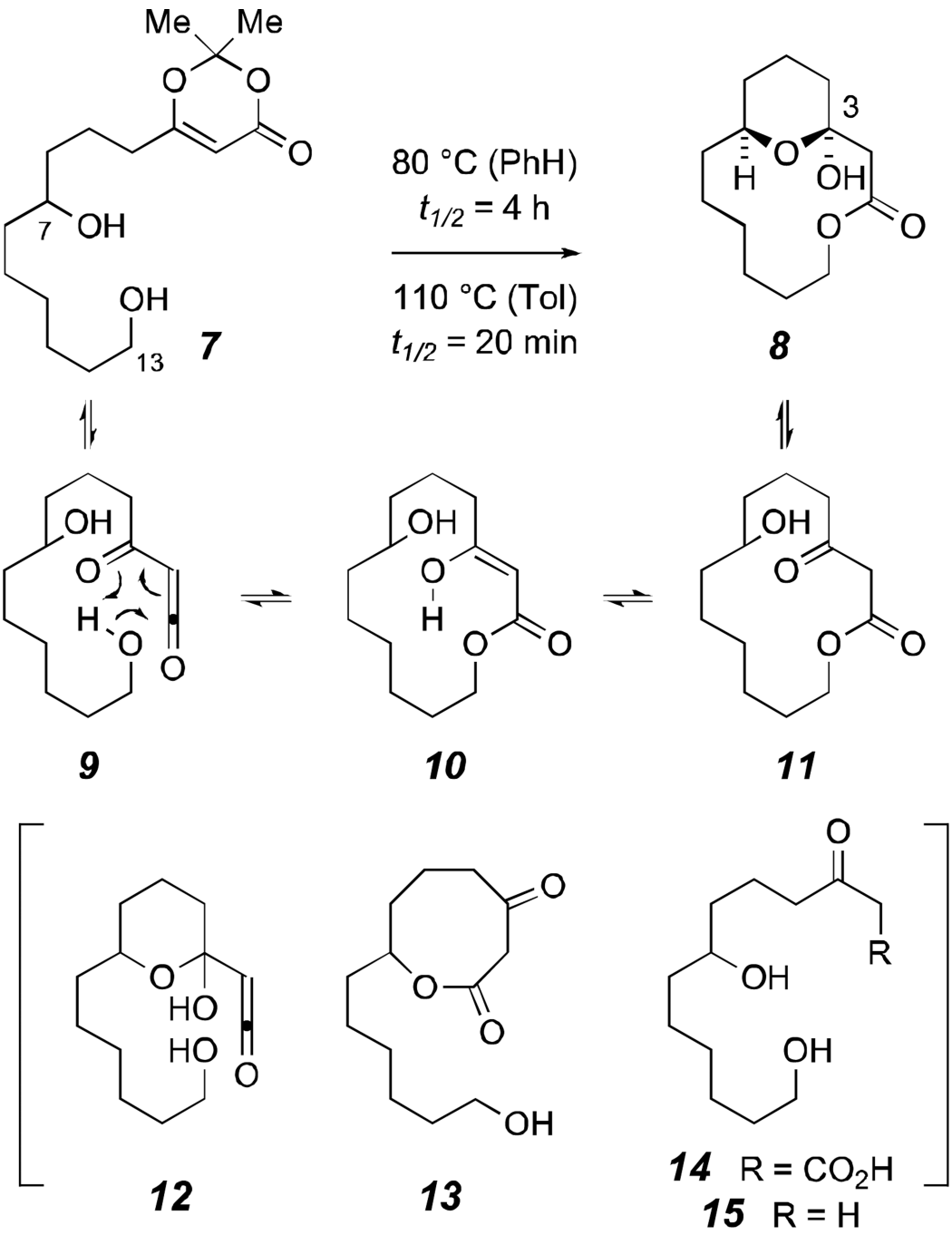


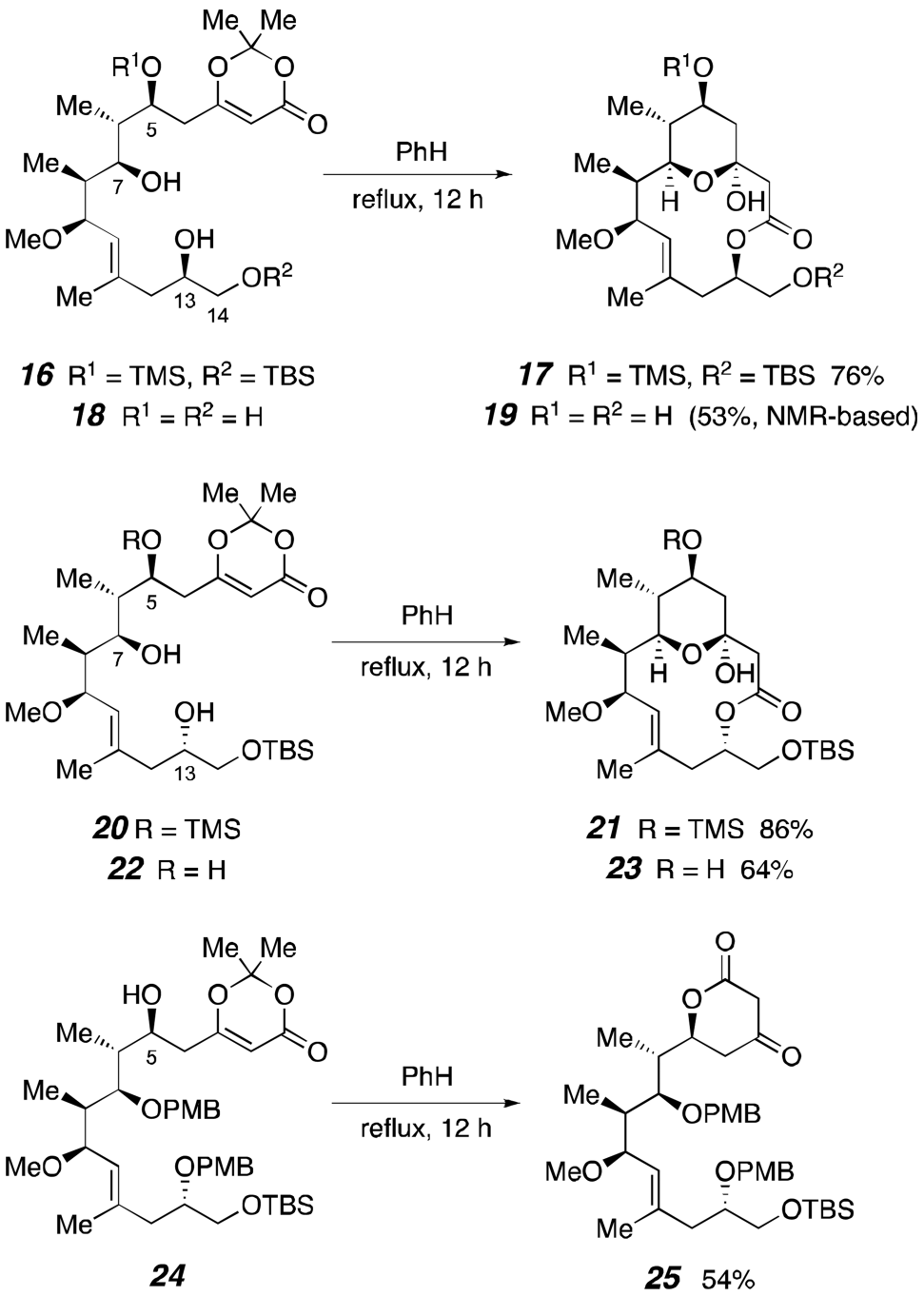
Figure 1.
Pyran-hemiketal containing macrolides.



Scheme 1.
β-Ketoester formation via acylketenes derived from dioxinones.

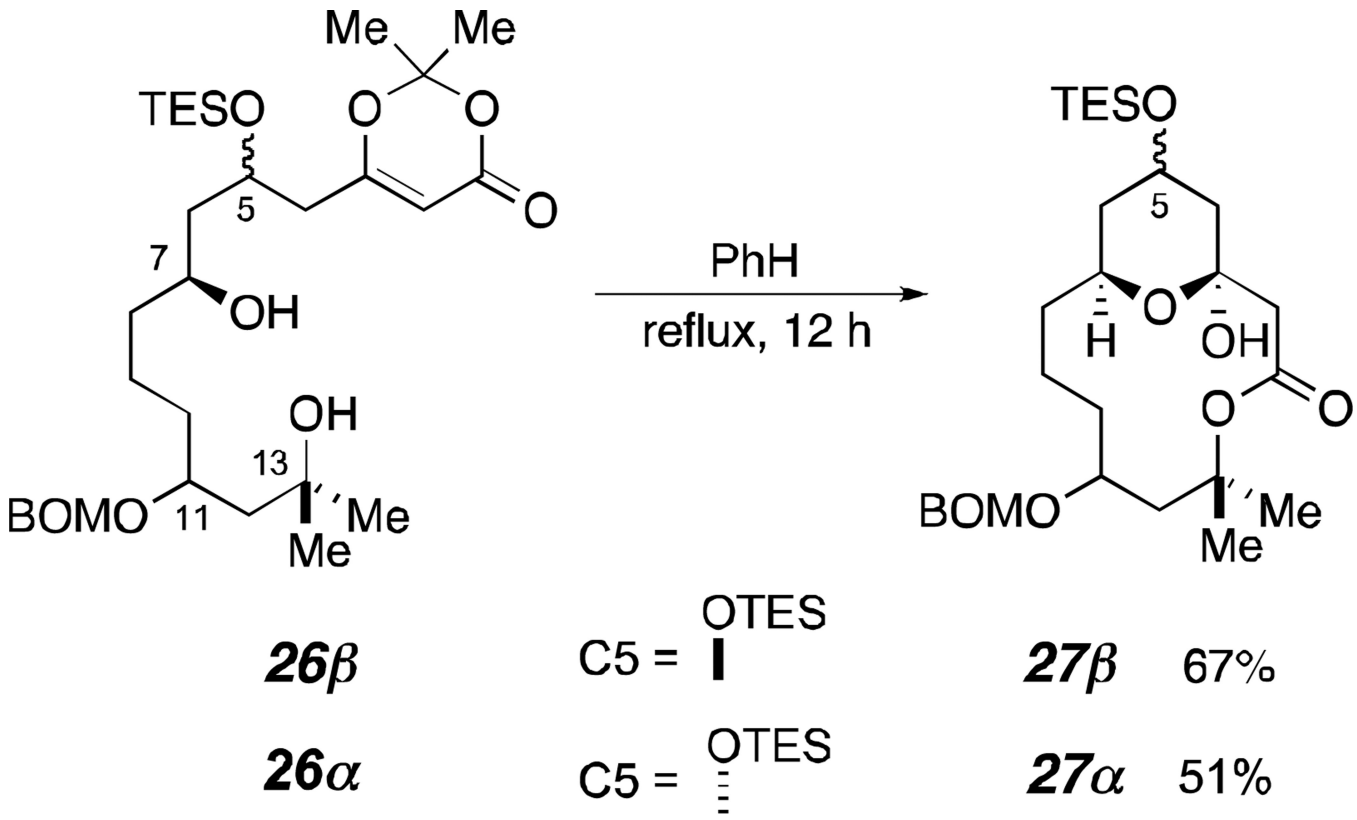


Scheme 2.
Dual macrolactonization/pyran formation *via* the acylketene diol **9**.



Scheme 3.

Dual macrolactonization/pyran formation of substrates used in the synthesis of callipeltoside A (**5**).[xv]



Scheme 4.

Dual macrolactonization/pyran-hemiketal formation of substrates relevant to the synthesis of lyngbyaloside B (**6**). [Each of **26β**, **26α**, **27β**, and **27α** was an *ca.* 1:1 mixture of C11-epimers.]