Synthetic Methods

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

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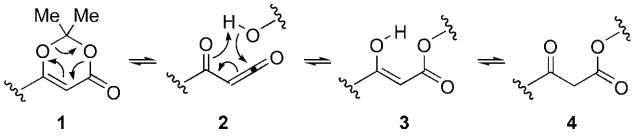
Acylketenes (Scheme 1, **2**) are often employed as electrophiles to trap alcohols to construct β-ketoesters (**4**) via the transient enols (**3**) produced by concerted addition[1] of the



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

hydroxylic nucleophile (Scheme 1).[2] Thermolysis of 1,3-dioxin-4-one derivatives (**1**) is the most common method used for the generation of **2**.[3] Boeckman and co-workers pioneered the application of these reactive species in the synthesis of complex molecules[4] such as macrocyclic lactones and lactams, which can be constructed by intramolecular reactions of hydroxy- or amino-containing acylketenes.[5]

As part of our research toward the synthesis of the complex pyran-containing macrolides callipeltoside A (Figure 1, **5**) and lyngbyaloside B (Figure 1, **6**), we have expanded the scope of this powerful transformation[6] by exploring the use of substrates containing multiple hydroxy groups.[7] The mechanism of addition of hydroxylic nucleophiles to acylketene renders this process highly regioselective, as reported herein for substrates containing up to four free hydroxy groups. 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**)[8] and lyngbyaloside B (**6**).[9]

We chose the prototypical substrate **7**[10] 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 (in a 9:1 ratio of **8** to its C3 anomer) and isolated in 80% yield.

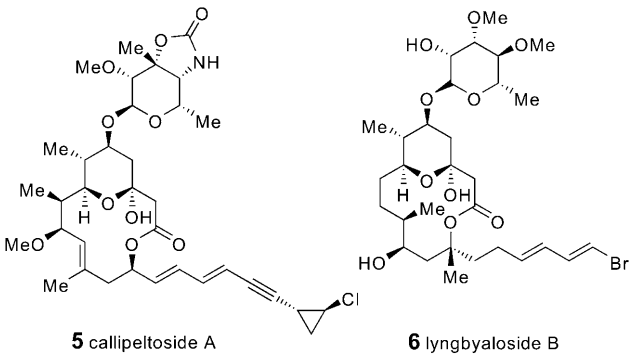
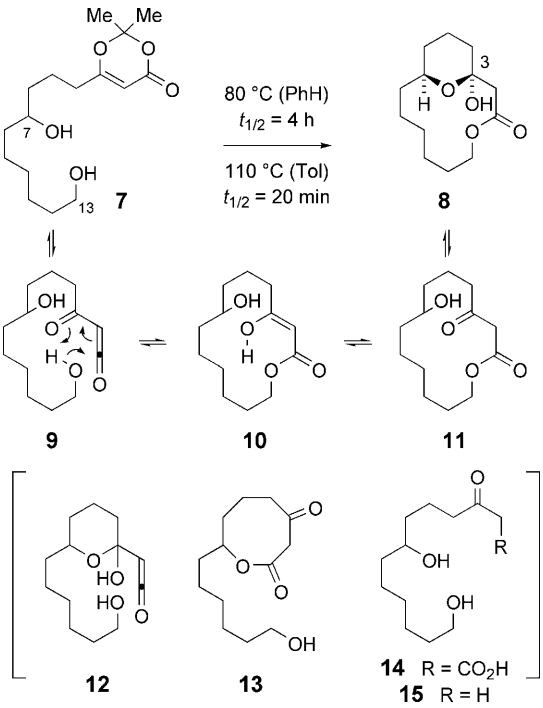


Figure 1. Pyran–hemiketal-containing macrolides.



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

Although we do not know the exact sequence of events that give rise to **8**, if the distal C13-hydroxy group in acylketene **9** were to add in a concerted 1,4-addition,[1] the enol-lactone **10** would be formed. Rapid tautomerization followed by hemiketal formation within ketone **11** accounts for formation of **8**. Several alternative intermediates or processes can be envisioned for the transformation of **7** to

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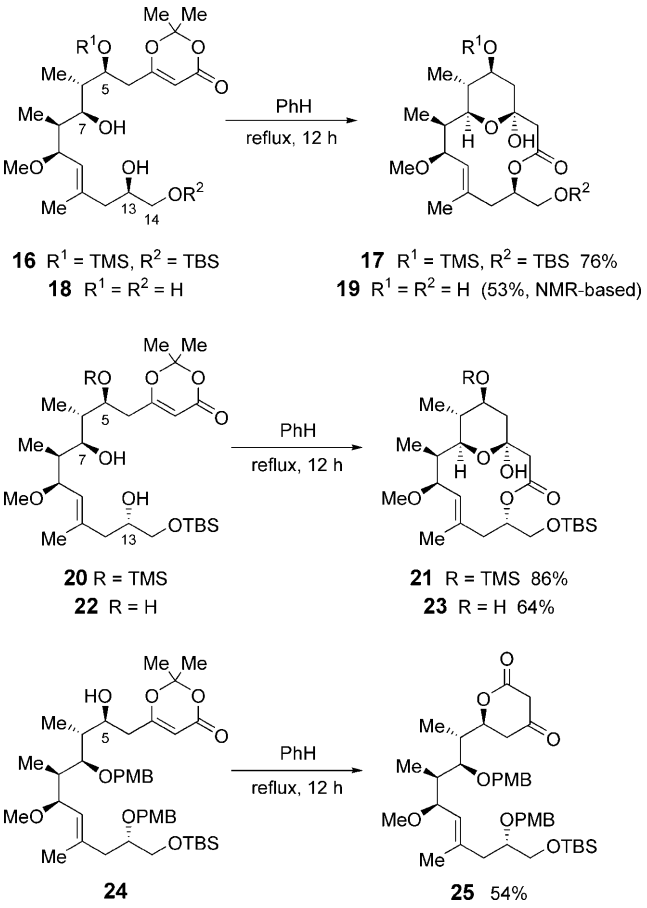
8: a) Hemiketal formation in **9** prior to lactonization would afford **12**, which could further cyclize to the macrolactone/pyran **8**. We presume that the acylketene **9** would lactonize considerably faster than the simple ketene **12** (for example, water reacts with acetylketene (AcCH=C=O) approximately 42000 times faster than with ketene (H_2C=C=O) itself).[11] Moreover, whereas no intermediates are involved in the transformation of **9** to **10**, hemiketal formation (**9** to **12**) likely requires catalysis by an external agent. Thus, we are inclined to believe that **12** is not involved in the process. b) Conjugate addition of the secondary carbinol to the enoate moiety in **10** could give rise directly to **8**. c) Trapping of the ketene by the secondary C7-hydroxy group in **9** would give rise to the eight-membered lactone **13**.[12] Although **13** was not detected, its further conversion into **8** by translactonization cannot be ruled out. d) Adventitious water could trap either of the ketenes **9** or **12** to afford the β-ketoacid **14**, which would be expected to decarboxylate to the methyl ketone **15**. When the benzene solvent was not predried, no methyl ketone **15** was detected. Even when excess water (0.5 M; biphasic system) was added at the outset to a solution of **7** in benzene (0.0003 M) that was then heated to reflux, lactone **8** was still the predominant product, but methyl ketone **15** was also detected (approximately 2:1 molar ratio by ^{1}H NMR spectroscopic analysis). When purified **8** was heated for 12 h in a benzene solution to which excess water had been added, no reaction occurred. When this experiment was repeated using D_2O, partial (mono- and di-) deuteration of C2 in **8** occurred.

The results listed under (d) are consistent with the reversion of lactone **8** to the ketone/enol pair **11** and **10**, but not reversion of **10** to the acylketene **9**. Conversely, both the $t_{1/2}$ values for the disappearance of **7** as well as the formation of methyl ketone **15** are consistent with an initial, rate-limiting thermolysis of dioxinone **7** to form the acylketene **9**.[13] Notably, **8** was formed in preference to **15**, even when the benzene reaction medium was saturated with water. Since the addition of a hydroxylic nucleophile to an acylketene is a concerted event, the relative O–H bond strengths in water (119 kcal mol^{-1}) versus those in alcohols (104–107 kcal mol^{-1}) are important.[14] We suggest that partial cleavage of the O–H bond, uniquely strong in water, renders hydrolysis considerably slower than alcoholysis. That is, lactonization within **9** is favored over the competitive hydrolysis reaction. We can further suggest that this preference is likely why acylketene macrolactonization reactions have proven to be so successful in late-stage (and often small-scale) constructions of complex molecules.[6]

We have used the dual cyclization process to synthesize callipeltoside A (**5**),[15] a natural product that was first synthesized using an acylketene cyclization to produce a late-stage β-ketomacrolactone intermediate.[16] Key experiments towards this end involved a series of polyhydroxylated substrates (Scheme 3). The 7,13-diol **16**[17] incorporates two free hydroxy groups and two that are capped as silyl ethers. Likewise, the C13-epimeric diol bis-silylether **20** was studied. Each of these dioxinone derivatives smoothly cyclized to its corresponding hemiketal **17** or **21** (in 76% and 86% yield, respectively) when refluxed in benzene solution for 12 h. We next examined the 5,7,13-triol substrate **22**, in which the C5-hydroxy group was exposed. This substrate also cyclized in good yield, to the lactone **23**. The six-membered pyranone ring that would have arisen by acylation of the C5-hydroxy group by the ketene was not detected.[18] To test whether pyranone formation was feasible, the thermolysis of the monoalcohol **24** was examined (Scheme 3). The pyranone **25** was isolated in 54% yield, establishing that the C5-hydroxy group is capable of trapping the acylketene in the absence of remote hydroxy groups that are geometrically suited for concerted addition.

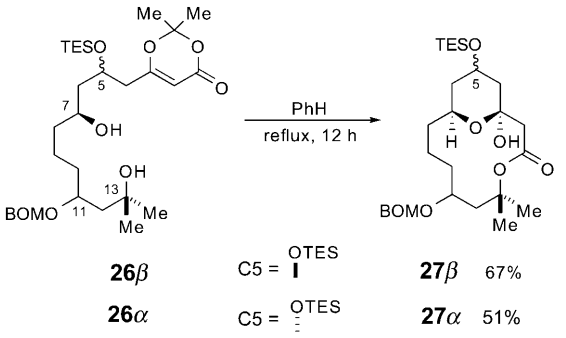


Scheme 3. Dual macrolactonization/pyran formation of substrates used in the synthesis of callipeltoside A (**5**). TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl[15]

Finally, the fully deprotected 5,7,13,14-tetrol substrate **18** was studied (Scheme 3). Remarkably, this substrate, with four free hydroxy groups, each, in principle, capable of participating in lactonization, cyclized to give the macrolactone **19** as the major product, in 53% yield. No other constitutional isomers were identified. Most interesting of all, perhaps, is the selective reaction of the secondary C13-hydroxy group in preference to the vicinal, primary C14-hydroxy group. To benchmark the inherent reactivity difference within a terminal vicinal diol, we treated an excess of 1,2-butanediol with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one in refluxing benzene or toluene and detected a 3:1 preference for formation of the primary β-ketoester. This result suggests that the regioselectivity of lactonization to the secondary C13-hydroxy group in **18** is conformational in origin, rather than a function of a

more inherent property, such as preferential hydrogen bonding or nucleophilicity, of a 1,2-diol moiety.

Lyngbyaloside B (**6**) incorporates both a pyran hemiketal and a tertiary macrolactone subunit, the latter an uncommon structural element in natural products. Macrolactonization reactions involving the OH group of a tertiary alcohol are also quite rare.[19] To test the feasibility of synthesizing a tertiary macrolactone, such as **6**, using the dual macrolactonization/pyran formation, we prepared the model C7/C13-diol substrates **26α** and **26β** (each as a 1:1 mixture of C11 epimers, Scheme 4).[10] In both substrates, competing eight-membered-lactone formation[12] was seen as a potential complication, if



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 approximate 1:1 mixture of C11 epimers. TES = triethylsilyl, BOM = benzyloxymethyl.

the tertiary C13-hydroxy group trapped the acylketene too slowly. It was also unclear whether the macrolactone product would be stable over the course of the reaction, since *tert*-butylacetoacetate thermally extrudes *tert*-butanol at essentially the same rate as acetone extrusion from dioxinones.[20]

In the event, heating **26β** or **26α** (benzene, 80 °C, 12 h) cleanly produced the desired lactone/pyran **27β** or **27α**, respectively, as the only isolable product. To our knowledge, these results constitute the most efficient macrolactonization involving a tertiary carbinol center, a fact that further demonstrates the power of acylketene methodology. When a solution of **27β** in toluene that had been doped with excess water was heated at reflux for 40 minutes (approximately two half-lives for acylketene formation from either dioxinones or *tert*-alkyl acetoacetates),[20] no decomposition was detected. It is likely that the internal trapping of the β-ketolactone as its hemiketal, thereby minimizing reversion to the reactive acylketene intermediate, contributes to the success of these transformations.

In summary, we have developed a process for dual macrolactonization/pyran–hemiketal formation through the trapping of thermally generated acylketenes by various diol substrates, thus expanding the scope of acylketene macrocyclizations. We have further exploited the concerted nature of the mechanism of the key cyclization event to regioselectively lactonize triol and tetraol substrates (Scheme 3, **22** and **18**, respectively). Additionally, the challenging macrolactonization of the tertiary alcohols **26β** and **26α** was achieved, which is encouraging in the context of ongoing studies into the synthesis of lyngbyaloside B. Broadly speaking, the dual cyclization transformation described here adds dimensionality to the Boeckman cyclization, particularly in the context of complex molecule synthesis.

Experimental Section

Synthesis of representative macrolactone/pyran **21**: Diol **20** (18 mg, 0.030 mmol) in benzene (2 mL) was added with a pipette to predried benzene (180 mL, dried azeotropically using Dean–Stark apparatus). The mixture was heated at reflux for 12 h and then allowed to cool to room temperature. Solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford macrolactone **21** (14 mg, 86%).

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

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