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Regioselective ring-closing metathesis on terpenoid acrylates and acrylamides

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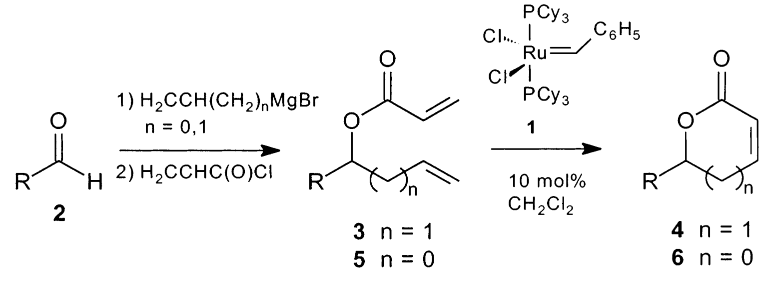
Abstract—A series of acrylate esters was prepared by treatment of representative terpenoid aldehydes with allyl or vinyl magnesium bromide followed by reaction with acryloyl chloride. In all cases, ring-closing metathesis (RCM) resulted in regioselective formation of unsaturated lactones through metathesis of the acrylate and terminal olefins. After condensation of farnesal with a primary amine, a parallel series of reactions led to formation of the corresponding lactam. © 2001 Elsevier Science Ltd. All rights reserved.

Ring-closing metathesis has become a well-established strategy for construction of a wide range of cyclic structures.[1] Various studies have shown that the most popular metathesis reagent, the Grubbs catalyst **1**, can tolerate a number of polar functional groups.[2] Its reactivity with any specific substrate is influenced by a combination of the steric and electronic effects of substituents on the reacting olefins as well as entropic factors,[3] but most ring-closing metathesis reactions have been reported on diene substrates that contain no other alkenes. Some recent studies[3a,4] have reported reaction of the two less-substituted olefins in trienes, but information on metathesis in systems containing multiple double bonds with varied substitution patterns is still limited.

In connection with our studies of farnesol derivatives,[5] a convenient method to append α,β-unsaturated lactones on a terpenoid skeleton was needed. The ring-closing metathesis of acrylates derived from allylic and homoallylic alcohols has been used to form unsaturated five- and six-membered ring lactones.[4c,6] However, at this time there is no literature precedent for such reactions in the presence of the other double bonds typical of common terpenoids. In this communication, we describe the construction of conjugated lactones on terpenoid templates via the regioselective ring-closing metathesis of acrylate esters.

As shown in Scheme 1, the general approach involved addition of allyl or vinyl magnesium bromide to a terpenoid aldehyde. The initial Grignard adduct could be quenched by addition of acryloyl chloride (Method A) or isolated as the alcohol and then esterified by treatment with acryloyl chloride (2 equiv.) and triethylamine (3 equiv.) (Method B).[7] In acrylates of the general structure **3** or **5** without additional olefins in the R group, treatment with Grubbs catalyst would be expected to afford an unsaturated lactone. But to test whether metathesis would be successful in the presence



Scheme 1.

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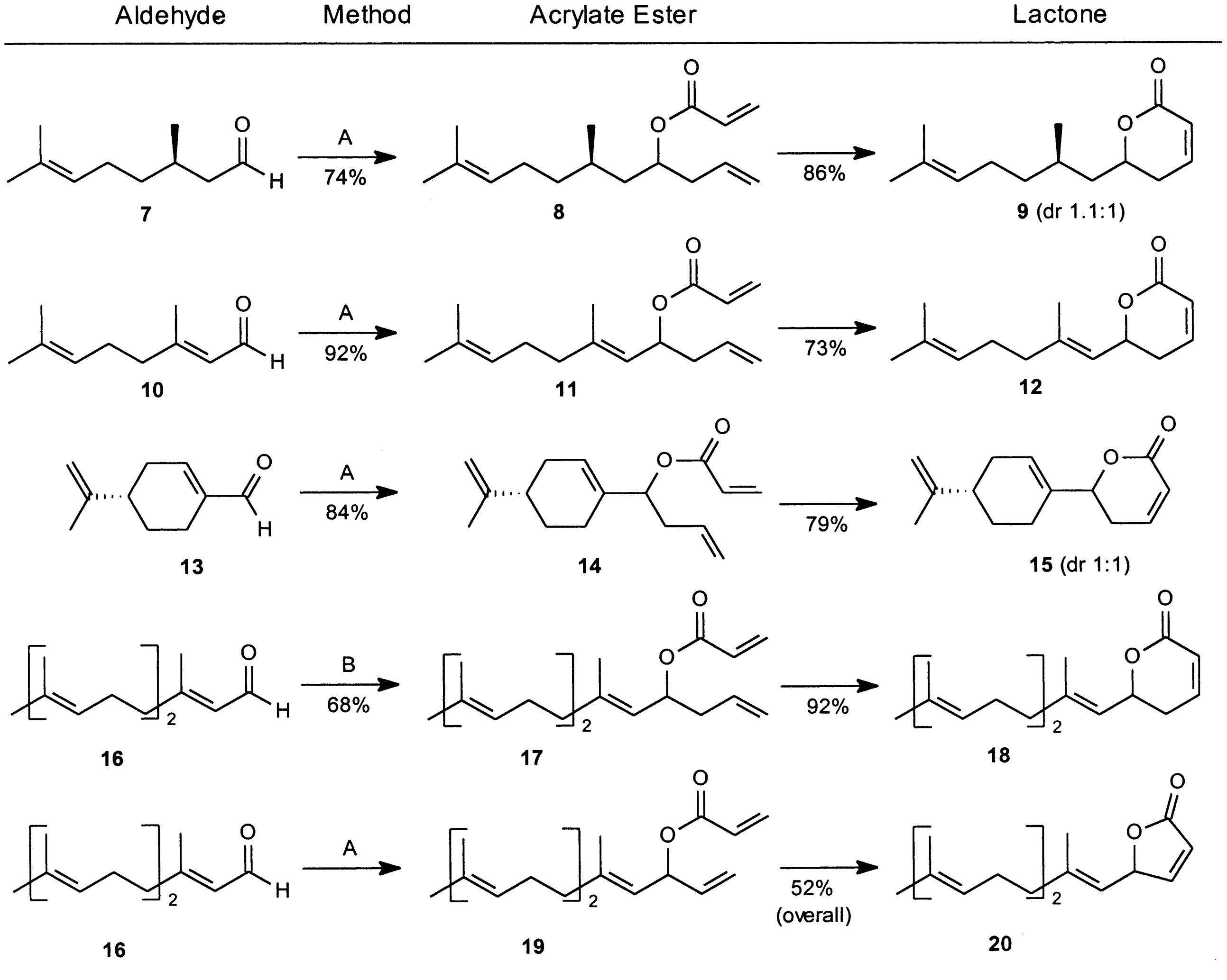
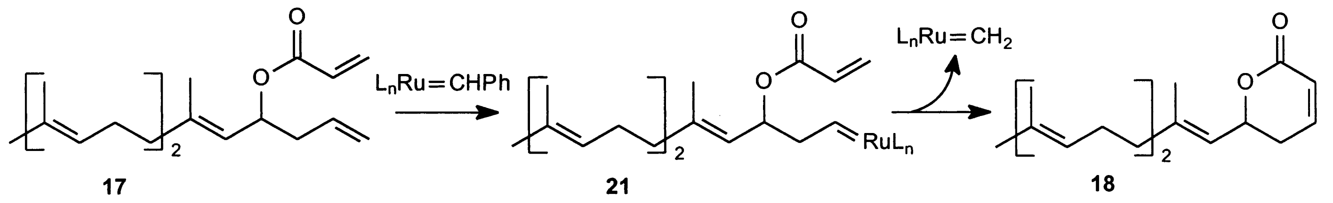
of the olefins typical of different terpenoids, this reaction sequence was applied to a small set of terpene aldehydes as shown in Table 1.

(*R*)-(+)-Citronellal (**7**), the simplest of the aldehydes examined with just one remote olefin, undergoes addition of allyl magnesium bromide and reaction with acryloyl chloride to give the desired ester **8** in good yield. Treatment of compound **8** with Grubbs reagent (**1**) gave the desired lactone **9** in 86% yield as a 1.1:1 mixture of diastereomers, with no detectable amounts of either regioisomeric metathesis product. The sequence worked just as well with aldehydes containing two olefins. With geranial (**10**), after allyl addition and formation of the acrylate ester **11**, metathesis gave the racemic lactone **12** in 73% yield as the only metathesis product.[8] With (*S*)-(−)-perillaldehyde (**13**), allyl addition and reaction with acryloyl chloride gave the ester **14** as the expected mixture of diastereomers. Once again only a single metathesis product was obtained (**15**) albeit as a 1:1 mixture of diastereomers. Finally, with farnesal (**16**) as the starting aldehyde, this sequence gave the pentaenes **17** from reaction with allyl magnesium bromide and **19** from reaction with vinyl magnesium bromide. In both cases, treatment with the Grubbs catalyst followed by DMSO[9] gave the desired cyclic product in very good yield despite the abundance of potential cyclization reactions.

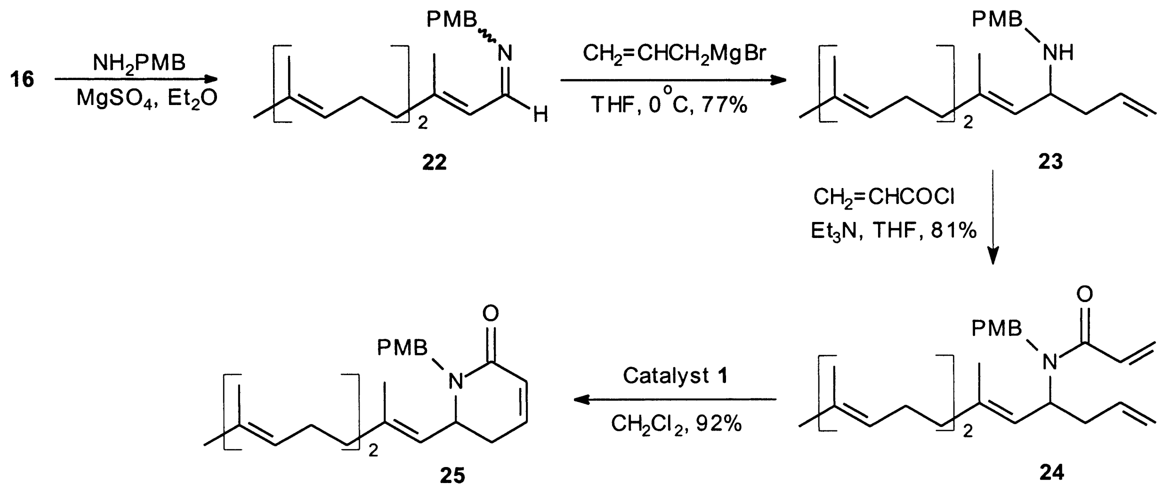
The regioselectivity reflected by the results summarized in Table 1 can be attributed to the preference of this catalyst for reaction at the less substituted olefins and the proximity of two monosubstituted olefins in each case. Trisubstituted olefins are known to undergo metathesis as shown by Hoye and Zhao in studies of linalool-derived dienes containing one tri- and one monosubstituted olefin.[10] However, they suggested that the trisubstituted olefin reacted with an alkylidene derived from an initial reaction of the catalyst with the monosubstituted olefin. By analogy, in the examples listed in Table 1, it is likely that metathesis is initiated by reaction of the monosubstituted olefin in a substrate such as pentaene **17** with the catalyst **1** to afford the alkylidene **21** followed by cyclization with the acrylate olefin to afford the lactone **18** (Scheme 2). This reaction sequence would generate the observed lactones and methylidene. The tri- and geminally disubstituted double bonds of the various terpenoids in Table 1 would neither initiate the olefin metathesis nor display competitive reactivity for the ruthenium alkylidenes. This is in agreement with Grubbs observation that the catalyst

Table 1. Synthesis and metathesis of terpenoid acrylates





Scheme 2.



Scheme 3.

1 could not initiate metathesis with *gem*-disubstituted olefins.[3a]

Given the positive results observed with formation of the farnesyl derivative **18**, we attempted to extend this approach to preparation of the corresponding lactam. Because an unprotected acrylamide has been found to undergo ring-closing metathesis in low yield,[11] a *p*-methoxybenzyl group was incorporated as a protecting group. As shown in Scheme 3, condensation of farnesal (**16**) with *p*-methoxybenzylamine afforded the intermediate imine **22**, which was treated with allyl magnesium bromide without isolation to afford the secondary amine **23**. After reaction with acryloyl chloride, the resulting amide **24** was treated with Grubbs catalyst to afford the lactam **25** in good yield.

In conclusion, metathesis of acrylate esters derived from different terpene aldehydes, as well as an acrylamide derived from farnesal, has been shown to afford lactone and lactam products in good yield and with excellent regioselectivity. Further studies on the application and biological activity of these terpenoid derivatives will be reported in due course.

Acknowledgements

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7. The acrylate esters **8**, **11**, **14** were purified by column chromatography on an aluminum oxide column. Compound **19** was used in the next step directly without further purification. All other intermediates and the final products were purified by column chromatography on silica gel.
8. Spectral data for compound **12**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (ddd, $J = 9.8$, 5.3, 3.1 Hz, 1H), 6.04 (ddd, $J = 9.8$, 2.3, 1.4 Hz, 1H), 5.35 (dq, $J = 8.5$, 1.2 Hz, 1H), 5.16 (ddd, $J = 9.8$, 8.6, 5.3 Hz, 1H), 5.11–5.04 (m, 1H), 2.46–2.31 (m, 2H), 2.16–2.02 (m, 4H), 1.72 (d, $J = 1.3$ Hz, 3H), 1.68 (d, $J = 1.0$ Hz, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 145.0,142.8, 132.0, 123.5, 121.8, 121.6, 74.9, 39.4, 29.9, 26.2, 25.7, 17.7, 16.8; HRMS calcd for $C_{14}H_{21}O_2$ (M^++H) 221.1542, found 221.1538.
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