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Synthesis of substituted butenolides by the ring closing metathesis of two electron deficient olefins: a general route to the natural products of paraconic acids class☆

N. Selvakumar,* P. Kalyan Kumar, K. Chandra Shekar Reddy and B. Chandra Chary

Department of Discovery Chemistry, Discovery Research, Dr. Reddy's Laboratories Ltd., Miyapur, Hyderabad 500 049, India

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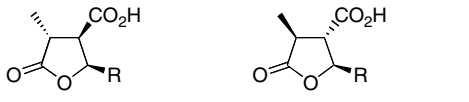
Abstract—A variety of allyl acrylates possessing electron-withdrawing groups undergo RCM using the second generation Grubbs' catalyst in the presence of a Lewis acid resulting in diverse butenolides in high isolated yields. This methodology provides a general route to the natural products of paraconic acids class, exemplified by a total synthesis of (±)-phaseolinic acid.

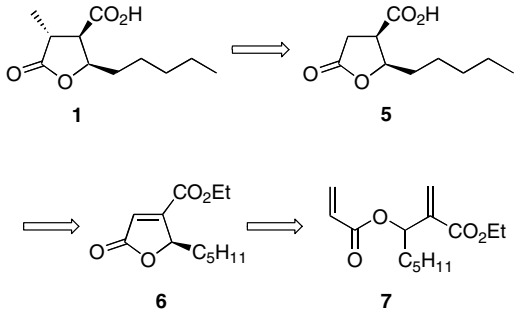
Paraconic acids are a group of highly substituted γ-butyrolactones isolated from different species of moss, lichens, fungi and cultures of *Penicillium* sp. (Fig. 1).[1] They possess either a methyl or a methylene group at the α-position and a carboxyl group at the β-position of the butyrolactone ring. However, they vary structurally with respect to the groups attached at the γ-position. The paraconic acids exhibit interesting biological activities such as antitumor, antifungal, and antibacterial.[2] Consequently, the synthesis of paraconic acids has attracted wide attention from synthetic chemists.[3] Herein, we report our initial efforts in this area culminating in an efficient and a general route to natural products of this class.

We envisioned that the β-carboxylated γ-butyrolactone skeleton in paraconic acids could conceivably be



1: R = C_5H_{11}, phaseolinic acid
2: R = $C_{13}H_{27}$, nephromopsinic acid
3: R = $C_{11}H_{23}$, nephrosteranic acid
4: R = $C_{13}H_{27}$, roccellaric acid

Figure 1.



Scheme 1. Retrosynthesis of compound **1**.

accessed via ring closing metathesis (RCM) of appropriate dienes (Scheme 1).[4] Since phaseolinic acid **1** had been prepared by methylating carboxylic acid **5**,[3e] we planned to obtain acid **5** from butenolide **6**, which in turn would be assembled from diene **7** using RCM as the key step. Diene **7** would be readily accessible by the acryloylation of the corresponding alcohol, which in turn would be available using a Baylis–Hillman reaction.[5] A literature search revealed that a β-carboxylated γ-butyrolactone had not been prepared using the RCM reaction.

In order to test the feasibility of a RCM reaction on the electron-deficient diene **7**, we turned our attention initially to cyclising the unsubstituted diene **9** as a model system (Scheme 2). Diene **9** was prepared by acryloylation of the known Baylis–Hillman adduct **8**.[5c] The preparation of 4,5-dialkyl butenolides has been reported

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* Corresponding author. Tel.: +91 40 2304 5439; fax: +91 40 2304 5438; e-mail: selvakumarn@drreddys.com

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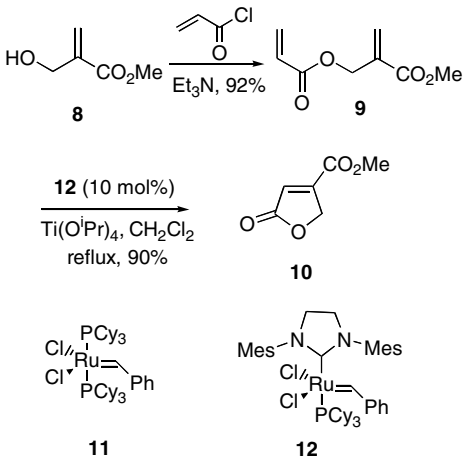
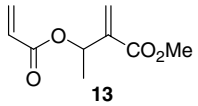
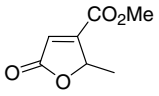
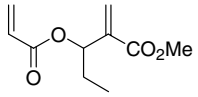
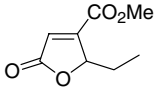
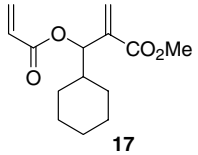
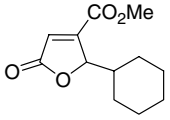
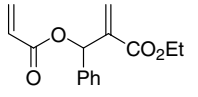
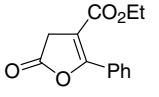
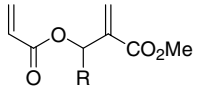
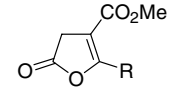
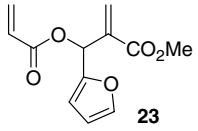
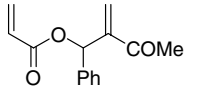
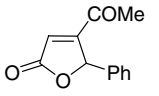
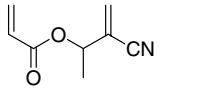


Scheme 2.

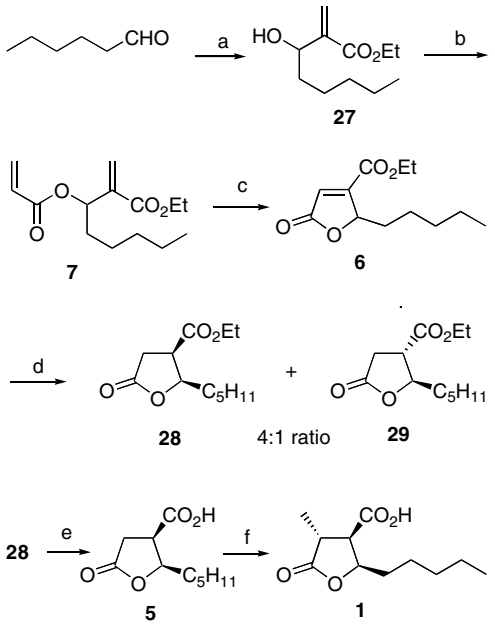
recently using the first generation Grubbs' catalyst **11** of the appropriate dienes wherein the dienes possess an alkyl group on one of the double bonds.[6] However, employing similar conditions for the RCM of diene **9**, with electron-withdrawing groups on the double bonds, did not result in even a trace of cyclisation product. In addition, attempted RCM of diene **9** using the second generation Grubbs' catalyst **12** also resulted in recovery of the starting material. At this stage, prompted by some literature reports that Lewis acids such as titanium tetraisopropoxide promote the RCM of many substrates,[7] we tried to perform the RCM in the presence of a Lewis acid. To that end, employing 10 mol % of Grubbs' second generation catalyst along with 10 mol % of $Ti(O^iPr)_4$ in dichloromethane, RCM of diene **9** resulted in the required cyclisation product **10** in 90% isolated yield.[8]

Table 1. Syntheses of 5-substituted butenolides

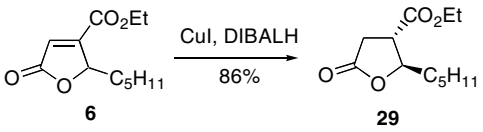
Entry	Starting material	Butenolide product	Yield (%)
1	 **13**	 **14**	84
2	 **15**	 **16**	87
3	 **17**	 **18**	88
4	 **19**	 **20**	84
5	 R = 4-nitrophenyl **21**	 R = 4-nitrophenyl **22**	77
6	 **23**	No RCM	0
7	 **24**	 **25**	78
8	 **26**	No RCM	0

Having identified appropriate experimental conditions, we turned our attention to substituted electron-deficient dienes in order to generalise the RCM method (Table 1).[9] Dienes **13** and **15** underwent a smooth RCM resulting in the corresponding alkyl substituted butenolides **14** and **16**, respectively. Likewise, the cyclohexyl substituted diene **17** gave **18** in a high yield. Successful closure was possible with aromatic substituents (entries 4 and 5), however, the double bond in the resultant butenolides **20** and **22** was found to have migrated to the β,γ-position presumably due to the extended conjugation. In order to bring further diversity at C-5, the RCM with the furan substituted diene **23** was attempted, but no trace of cyclisation product was found. Next, we explored the RCM reaction on dienes possessing different electron-withdrawing groups such as ketone and nitrile in place of the ester. Thus, keto-diene **24**, gave the required product **25** in good yield. However, all our attempts with diene **26**, possessing a nitrile group as the electron-withdrawing group, resulted only in recovery of starting material.

Having generalised the RCM reaction of the electron deficient dienes, we turned our attention to the synthesis of phaseolinic acid **1** (Scheme 3). The known Baylis–Hillman adduct **27**,[5b] obtained from ethyl acrylate and hexanal, was acryloylated to afford diene **7**, which underwent a smooth RCM reaction leading to the cyclisation product **6**.[10] Catalytic hydrogenation of butenolide **6** using Pd/C in ethyl acetate resulted in a 1:2 diastereomeric mixture of *cis* and *trans* butyrolactones **28** and **29**, respectively, which was easily separated by column chromatography. Apart from the spectral data, 1D NOE experiments revealed a strong interaction for



Scheme 3. Reagents and conditions: (a) Ref. 5b; (b) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 95%; (c) **12**, $Ti(O^iPr)_4$, 50 °C, 87%; (d) 10% Pd–C, H_2, EtOAc, 84% (combined yield, 1:2 ratio) or 10% Pd–C, ammonium formate, MeOH, reflux, 83% (combined yield, 4:1 ratio); (e) 6 N HCl, dioxane, reflux, 91%; (f) $NaN(TMS)_2$, MeI, THF, −78 °C.



Scheme 4.

the cis vicinal protons in the isomer **28**, which provided further evidence for the identity of isomers **28** and **29**.[11] After considerable efforts to improve the ratio of the isomers in favour of the cis isomer **28**, we discovered that transfer hydrogenation with ammonium formate resulted in an acceptable ratio of 4:1. The total synthesis of phaseolinic acid was completed following the reported protocol.[3e] Thus, cis diastereomer **28** was converted to (±)-phaseolinic acid **1** by hydrolysis followed by methylation. The spectral data of the synthetic material were comparable to that of reported values.[3a]

It is interesting to note that other natural products of the paraconic acids class could be synthesised following a similar sequence. Thus, the total synthesis of nephrosteranic acid **3** could be achieved from the *trans* alcohol analogous to **29** obtained using dodecanal as the aldehyde in the Baylis–Hillman reaction instead of hexanal (Scheme 3).[12] In a similar way, using tetradecanal as the aldehyde would pave the way for the total synthesis of roccellaric acid **4**. As the syntheses of these natural products **3** and **4** require the *trans* alcohol analogous to **29**, we wished to identify a method to obtain the *trans* alcohol exclusively. To that end, after considerable attempts, we discovered that a 1,4-hydrogen addition using DIBAL-H in toluene afforded the required trans isomer exclusively (Scheme 4). The total syntheses of nephrosteranic acid **3** and roccellaric acid **4** will be the subject of future publications from our laboratory.

In conclusion, the RCM reaction of highly electron-deficient dienes has been achieved resulting in diverse butenolides possessing electron-withdrawing groups at C-4. It is important to note that dienes having two electron-deficient olefins underwent smooth RCM under the identified experimental conditions. One such butenolide product **6** served as the starting material for the total synthesis of (±)-phaseolinic acid **1**.

Acknowledgements

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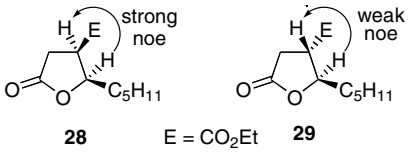
8. *General experimental procedure for RCM*: A two-neck flask equipped with a condenser was flame dried in vacuo and charged successively with a solution of the diene (0.01 M) in dry DCM followed by titanium tetraisopropoxide (10 mol %) under argon. To this solution was added dropwise a 0.01 M solution of catalyst **12** (10 mol %) in dry DCM over 12 h at reflux using a syringe pump. The mixture was stirred at reflux for a further 24 h. The reaction mixture was allowed to cool and then washed with water, brine and dried. The solvent was removed in vacuo and the residue was purified by silica gel chromatography to separate the desired cyclisation product from the recovered starting material.
9. The starting dienes for entries 1–6 were prepared from the corresponding acrylates and appropriate aldehydes using Baylis–Hillman reactions followed by acryloylation. Following the same sequence, the dienes in entries 7 and 8 were prepared from methyl vinyl ketone and acrylonitrile, respectively.
10. *Selected spectral data for compound* **6**: (oil) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.64 (d, $J = 1.9$ Hz, 1H), 5.21 (ddd, $J = 8.1$, 3.0 and 2.2 Hz, 1H), 4.38–4.30 (m, 2H), 2.16–2.08 (m, 1H), 1.69–1.60 (m, 1H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.45–1.25 (m, 6H), 0.90–0.87 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.0, 161.0, 157.7, 126.6, 82.6, 62.1, 32.4, 31.3, 24.3, 22.3, 14.0, 13.9. IR (neat): 1769, 1728, 1223, 1156 cm^{-1}.
11. The spectral data of compounds **28** and **29** were identical to reported values. Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Chem. Commun.* **1996**, 1289–1290.



12. For a synthesis of nephrosteranic acid **3**, see: Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4097–4099.