JOC The Journal of Organic Chemistry

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Base-Stimulated 1,2-, 1,4-, and 1,6-Eliminations in Suitably Substituted Alkylidenesuccinates Leading to Natural and Unnatural Conjugated Alkenyl(methyl)maleic Anhydrides

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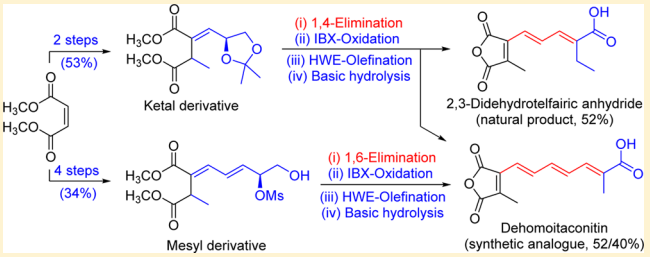
Supporting Information

ABSTRACT: With dimethyl maleate as the starting material, facile stereoselective syntheses of natural and unnatural conjugated alkenyl(methyl)maleic anhydrides have been described. The key reactions were base-endorsed novel 1,2-, 1,4-, and 1,6-eliminations in the corresponding alkylidenesuccinate derivatives. The 1,2-eliminations in cyclic carbonate and sulfite by regioselective abstraction of methine protons with the respective release of CO_2 and SO_2 provided a conjugated ketone product. The characteristic 1,4- and 1,6-elimination reactions with respective release of acetone and mesylate furnished the corresponding unsaturated alcohols. The obtained allylic alcohols were transformed into conjugated alkenyl(methyl)maleic anhydrides via oxidation followed by a Horner−Wadsworth−Emmons reaction pathway in very good yields. The mechanistic aspects involved in these significant elimination reactions have also been described in brief.



INTRODUCTION

Maleic anhydride is a vital functionality in chemistry from both basic and applied points of view.[1] A large number of alkyl(methyl)maleic anhydrides have been isolated as natural products and reported to exhibit a broad range of biological activities.[2] More specifically, the dianionic form of chaetomellic acid A (tetradecyl(methyl)maleic anhydride) is a potent ras farnesyl-protein transferase (RFTase) inhibitor, as it contains both the essential hydrophilic and hydrophobic units to appropriately bind and deactivate the responsible enzyme.[3] Vederas and co-workers reasoned and synthesized the unnatural farnesyl(methyl)maleic anhydride, which exhibited 7-fold enhancement in RFTase inhibition in comparison to chaetomelic acid A.[4] A cursory literature search in this context revealed that three yellow crystalline conjugated alkenyl(methyl)maleic anhydrides have also been isolated as the natural products (Figure 1).[5−7] The itaconitin, graphenone, and 2,3-didehydrotelfairic anhydride were respectively isolated from the cultures of *Aspergillus itaconicus*,[5] mycobiont *Graphis scripta*,[6] and *Xylaria telfairii* Berk.[7] Retrobiogenetically, nature might be designing these novel multifunctional architectures from pyruvic acid in a stepwise fashion. To date, syntheses of those naturally occurring alkenyl(methyl)maleic anhydrides have not been reported. However, the itaconitin side chain is known to undergo an intramolecular cyclization to form the aryl ring.[5] Accordingly, these conjugated alkenyl(methyl)maleic anhydrides are anticipated to be the sensitive compounds. Hence, the real challenge in total synthesis of these delicate targets is in creating geometrically pure conjugated alkenyl chains and conserving them throughout the total synthesis. In continuance with our the past two decades of synthetic studies on cyclic anhydrides and their derivative chemistry,[8] we herein report the first total synthesis of the natural product 2,3-didehydrotelfairic anhydride along with analogous unnatural conjugated alkenyl(methyl)maleic anhydrides via novel 1,2-, 1,4-, and 1,6-elimination reactions in alkylidenesuccinate derivatives (Schemes 1−10).

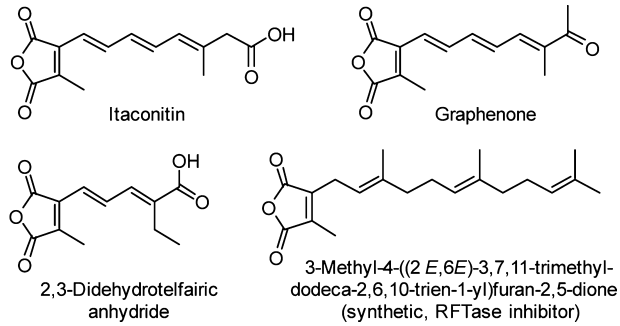


Figure 1. Natural and unnatural alkenyl(methyl)maleic anhydrides.[4−7]

RESULTS AND DISCUSSION

Retrosynthetically, the unknown unsaturated aldehydes portrayed in Figure 2 would be potential building blocks for the synthesis of target compounds. Among these, dimethyl formyl(methyl)maleate is still elusive for stability reasons. Syntheses of the other two requisite unsaturated aldehydes were planned from the readily available dimethyl maleate via a

Received: December 24, 2013
Published: March 4, 2014

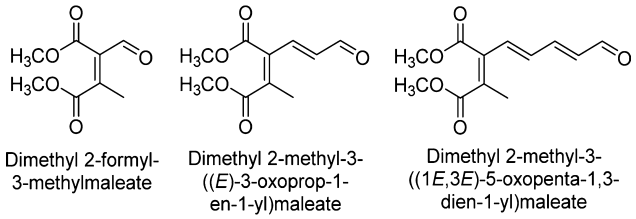


Figure 2. Potential precursors for the synthesis of natural and unnatural conjugated alkenyl(methyl)maleic anhydrides.

Wittig reaction, allylic α-methylation, ketal deprotection, 1,4- and 1,6-elimination, and oxidation route. The reaction of an Wittig reagent generated in situ from tributylphosphine and dimethyl maleate (**1**)[9] with commercially available (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde in THF at room temperature furnished a silica gel column chromatographically inseparable *E*/*Z* mixture of the required coupling product **2** in 72% yield (*E*:*Z* = 19:1, by ^{1}H NMR) (Scheme 1). As expected, the vinylic proton in the major *E* isomer appeared downfield due to the *peri* interaction with an ester carbonyl group. Base-induced α-methylation of compound **2** was performed using NaHMDS and methyl iodide to obtain the geometrically pure product **3** in 73% yield. In the course of the aforementioned methylation studies, we noticed the direct formation of a small amount of desired product **4** (nearly 5%). We systematically studied the aforementioned exotic transformation of compound **3** into product **4** by using various bases, and the results obtained are summarized in Table 1. Rewardingly, LiHMDS was most effective at −78 °C and provided the targeted E2′-1,4-elimination product **4** in 71% yield (Table 1, entry 7). The base NaHMDS was found to be relatively less effective for the Na^+ ion size and its complex forming ability issues (Table 1, entry 9, 42% yield).

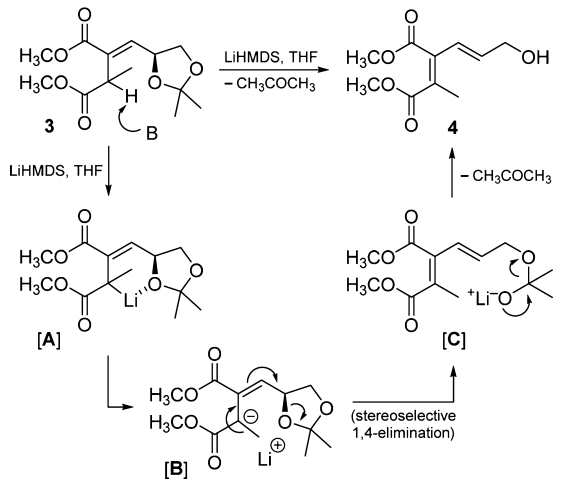
A plausible mechanism for the present ketal to allylic alcohol transformation is described in Scheme 2. LiHMDS abstracts an acidic methine proton and forms the cyclic six-membered lithium complex [**A**].[10] The complex [**A**] transforms into the allylic carbanionic intermediate [**B**], in which the formed carbanion delocalizes and system undergoes a concerted E2′-1,4-elimination process[11] to yield the intermediate [**C**]. Finally, intermediate [**C**] releases acetone as a leaving group, generating the α,β-unsaturated alcohol **4**. In this transformation, the carbanion stereoselectively delocalizes in a α,β-unsaturated carbonyl system to gain the extension of conjugation along with generation of a tetrasubstituted carbon−carbon double bond.

Table 1. Base-Induced 1,4-Elimination Studies in Cyclic Ketal 3

entry	base (amt, equiv)	temp, °C	time, h	yield, %
1	Et_3N (3.00)	reflux	12	NR[a]
2	DBU (3.00)	reflux	12	CM[b]
3	NaH (2.00)	25	5	5
4	*n*-BuLi (2.00)	−78	1.5	CM
5	*t*-BuLi (2.00)	−78	1.5	CM
6	LDA (2.00)	−78	1.5	CM
7	LiHMDS (2.00)	−78	1.5	71
8	LiHMDS (1.50)	−78	1.5	67
9	NaHMDS (2.00)	−50	1.5	42
10	KHMDS (2.00)	−78	1.5	CM

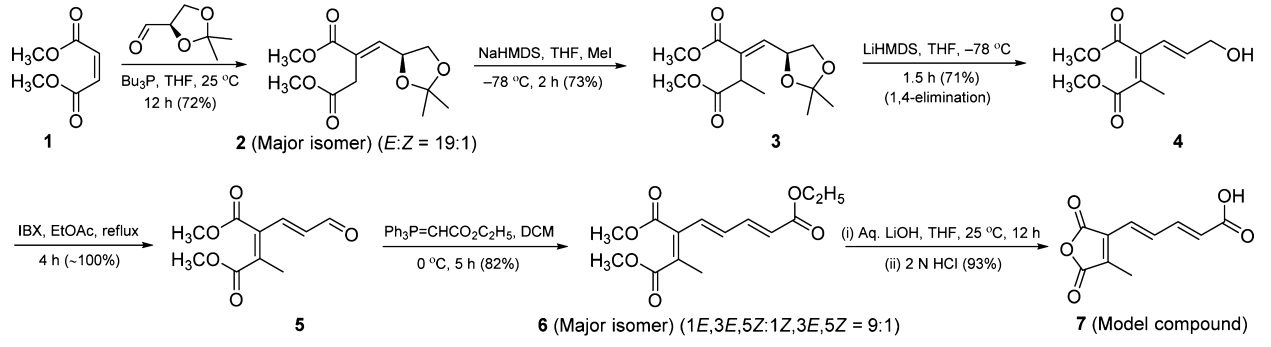
[a]NR = no reaction. [b]CM = complex mixture (by TLC).

Scheme 2. Plausible Mechanism for LiHMDS-Induced Cleavage of Ketal



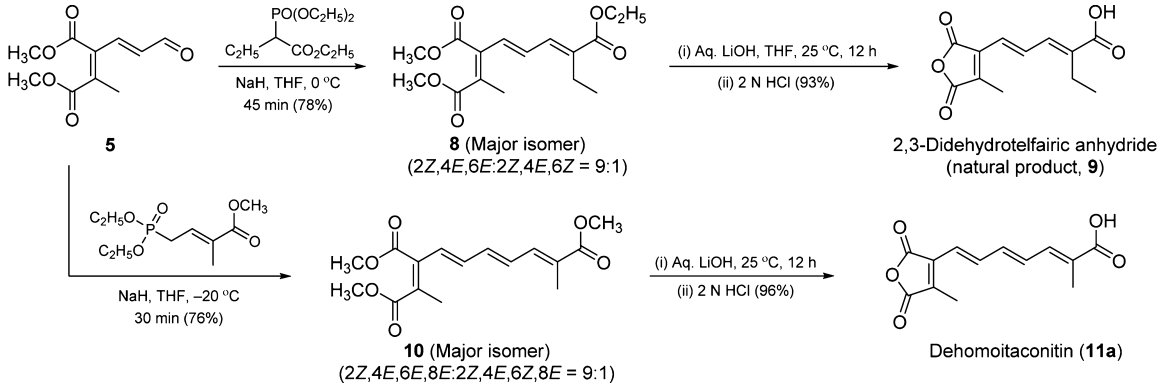
The present one-pot transformation of ketal to allylic alcohol is characteristic, as it beneficially covers the otherwise required ketal deprotection, selective primary alcohol protection, transformation of secondary alcohol into a good leaving group, requisite 1,4-elimination, and the final deprotection step. A similar migration of a carbon−carbon double bond involving the cleavage of ketal is known in related sulfones.[12] The observed base-stimulated intramolecular elimination reactions of the ketal moiety via the Li chelation process would be feasible in several other structurally related systems

Scheme 1. Base-Promoted Unusual Cleavage of Ketal with 1,4-Elimination of Acetone Targeting Alkenyl(methyl)maleic Anhydride



dx.doi.org/10.1021/jo402857r | J. Org. Chem. 2014, 79, 2538−2546

Scheme 3. Synthesis of Naturally Occurring 2,3-Didehydrotelfairic Anhydride and Dehomoitaconitin

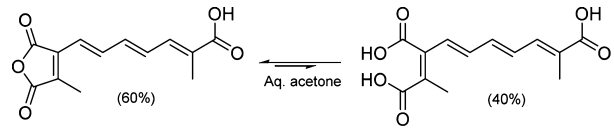


and can be used for concise and efficient synthesis of many other complex target compounds.

The allylic alcohol **4** on 2-iodoxybenzoic acid (IBX) oxidation formed a requisite building block, the α,β-unsaturated aldehyde **5**, in almost quantitative yield. We initially studied the reactions of several unstabilized Wittig reagents with unsaturated aldehyde **5** and noticed the complete decomposition of reaction mixtures. Providentially, the Wittig reaction of the stabilized ylide ethyl 2-(triphenyl-λ^5-phosphanylidene)-acetate with aldehyde **5** was very clean and provided a silica gel column chromatographically inseparable mixture of geometric isomers of the essential triester **6** in 82% yield (1*E*,3*E*,5*Z*:1*Z*,3*E*,5*Z* = 9:1, by ^{1}H NMR). As expected, the stabilized ylide provided the corresponding 1*E*,3*E*,5*Z* isomer as a major product. Basic hydrolysis of the triester **6** followed by acidification exclusively delivered the model compound **7** in 93% yield (Scheme 1). In the hydrolysis reaction, the minor 1*Z*,3*E*,5*Z* isomer also rearranged into the thermodynamically more stable 1*E*,3*E*,5*Z* isomer. Similarly, an appropriate Horner–Wadsworth–Emmons (HWE) reaction of ethyl 2-(diethoxyphosphoryl)butanoate with aldehyde **5** followed by hydrolysis of the resulting triester **8** furnished the geometrically pure natural product 2,3-didehydrotelfairic anhydride (**9**) in 73% yield (Scheme 3). The analytical and spectral data obtained for natural product **9** were in complete agreement with the reported data,[7] and they confirmed our geometric assignments of newly formed carbon–carbon double bonds. Starting from dimethyl maleate, the natural product **9** was obtained in six steps with 27% overall yield. Yet another suitable HWE reaction of aldehyde **5** with methyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate[13] followed by the hydrolysis of formed triester **10** offered the unnatural dehomoitaconitin (**11a**) in 73% yield over two steps. Fortunately, the model compund **7** and the natural product **9** were found to be fairly stable in anhydride form, while as anticipated the compound **11a** with an additional carbon–carbon double bond in conjugation was not stable in acetone for longer times. The immediately scanned ^{1}H NMR spectrum of compound **11a** in acetone was very clean. However, ^{1}H and ^{13}C NMR spectra of the same sample scanned after 2 h and once again after 2 days indicated that the anhydride **11a** in acetone is in equilibrium with its dicarboxylic acid **11b** (3:2) (Scheme 4).

In the next part of the study, we planned to synthesize another building block from Figure 2, dimethyl 2-methyl-3-((1*E*,3*E*)-5-oxopenta-1,3-dien-1-yl)maleate, via the corresponding 1,6-elimination approach. The most important "π spacer

Scheme 4. Anhydride–Dicarboxylic Acid Equilibrium in Acetone

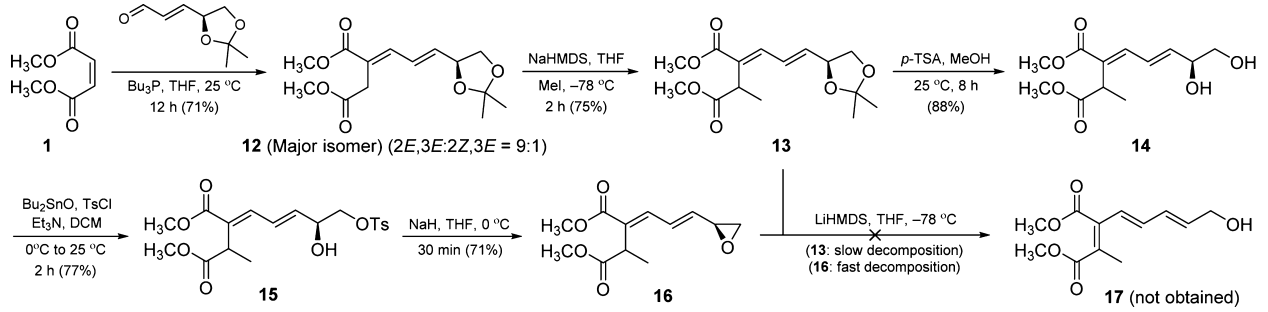


units" involved in 1,6-elimination reactions are aromatic/heteroaromatic rings, triple bonds, and double bonds.[14−17] Most such reactions have been reported with aryl rings and a few reactions with triple bonds, as the separating units involve obvious well-ordered transition states.[14,15] Only a handful of reactions with double bonds as the spacer units in substrates bearing cyclic backbones are known in the literature.[16] Otera et al. proposed a unique 1,6-elimination reaction with double bonds as spacer units in an open-chain system.[17] The essential requirement for such a type of 1,6-elimination reaction is a proper connection between the formed carbanion and remotely placed leaving group through the appropriate alkenyl units.

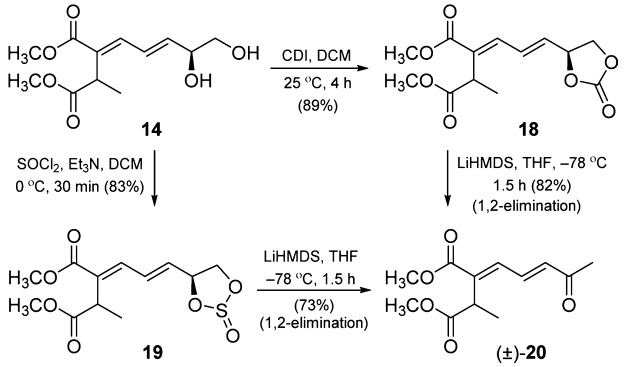
The tributylphosphine-induced Wittig reaction of dimethyl maleate (**1**) with (*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-acrylaldehyde[18] gave the coupling product **12** in 71% yield as a silica gel column chromatographically inseparable mixture of *E* and *Z* isomers (2*E*,3*E*:2*Z*,3*E* = 9:1, by ^{1}H NMR) (Scheme 5). Compound **12** (2*E*,3*E* isomer) has been also synthesized earlier via catalytic carbenoid insertion into the olefinic C–H bond of allylic ylide,[19] and we confirmed the geometry of our product by comparison of NMR data. The α-methylation of compound **12** was performed by using NaHMDS and methyl iodide to give the geometrically pure product **13** in 75% yield. Unfortunately, the reaction of ketal **13** with LiHMDS at −78 °C resulted in slow decomposition and failed to deliver the anticipated product **17** via the possible 1,6-elimination pathway. In this case the formation of a stable cyclic lithium complex is forbidden due to ring size and geometry issues. Ketal **13** on usual *p*-TSA deprotection provided the diol **14** in 88% yield. The diol **14** was transformed to epoxide **16** via the corresponding primary monotosylate **15** (55% over two steps). Oxirane **16** also underwent excessive decomposition on treatment with LiHMDS. As illustrated in Scheme 6, diol **14** was then converted into the corresponding cyclic carbonate **18** and sulfite **19** in 89% and 83% yields, respectively. Compounds **18** and **19** on treatment with LiHMDS also failed to deliver the required product **17** via a 1,6-elimination sequence. Instead, both reactions exclusively provided the unsaturated ketone

dx.doi.org/10.1021/jo402857r | J. Org. Chem. 2014, 79, 2538–2546

Scheme 5. Synthesis and an Attempted Base-Promoted 1,6-Eliminative Cleavage of Ketal and Oxirane Units

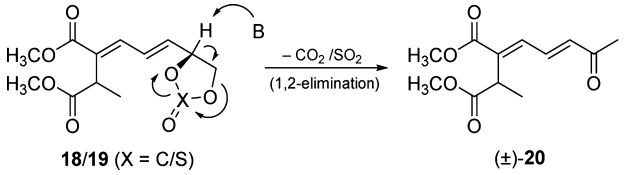


Scheme 6. Remarkable Base-Promoted 1,2-Eliminations



product **20** in 82% and 73% yields, respectively. Mechanistically, LiHMDS regioselectively abstracts the alternative acidic methine protons present on the cyclic carbonate and sulfite moieties, which on concurrent 1,2-eliminations respectively release CO_2 and SO_2 to form product **20** (Scheme 7). In these

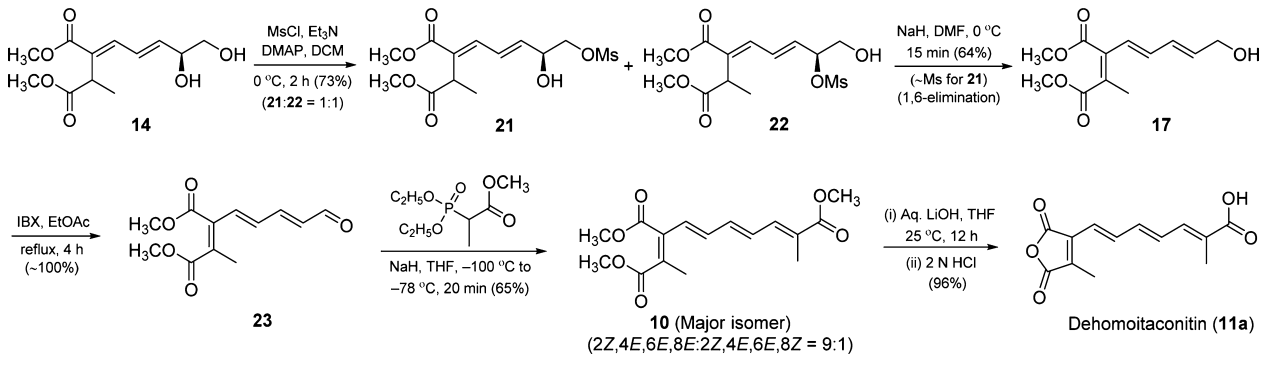
Scheme 7. Proposed Mechanism for the Unusual Cleavages of Cyclic Carbonate and Sulfite



cases the release of strain in cyclic carbonate and sulfite by 1,2-elimination is the more preferred process and the eliminations are significant from a basic chemistry point of view.

Finally, in search of a suitable substrate to enforce the 1,6-elimination reaction, we decided to transform diol **14** into the corresponding mesylate derivative (Scheme 8). Diol **14** on treatment with methanesulfonyl chloride gave an ~1:1 mixture of the corresponding primary and secondary mesylates **21** and **22** in 73% yield. We presume that initially the primary alcohol forms the corresponding mesylate **21** and an in situ partial intramolecular migration results in secondary mesylate **22** for stability reasons. Such a type of an in situ intramolecular vicinal migration is in accordance with the literature precedents.[8b,20] The mixture of primary and secondary mesylates **21** and **22** was separated by using silica gel column chromatography for characterization purposes, and their structures were established with the help of NMR data obtained for diol **14** and tosylate **15**. Initially, we decided to directly perform the base-promoted 1,6-elimination on a freshly prepared mixture of mesylates **21** and **22** due to stability and yield concerns. Rewardingly, the mixture of mesylates **21** and **22** on treatment with sodium hydride underwent a smooth 1,6-elimination process and delivered the desired unsaturated alcohol **17** in 64% yield. In a control experiment we also treated the column-purified primary mesylate **21** with sodium hydride and obtained the desired 1,6-elimination product **17** in almost the same yield. In both reactions specified above, the primary mesylate **21** transforms into the secondary mesylate **22** under basic conditions and then undergoes a requisite 1,6-elimination process. The formation of the conjugated polyene chain may be a plausible driving force in the present 1,6-elimination reaction. We believe that this is the full-proof 1,6-elimination reaction in a flexible acyclic system involving double-bond spacers. Alcohol **17** on IBX oxidation produced yet another building block, the unsaturated aldehyde **23**, also in ~100% yield. We studied the HWE reaction of the ylide methyl 2-(diethoxyphosphoryl)propanoate with aldehyde **23** at −78 °C and noticed the partial

Scheme 8. Base-Induced 1,6-Elimination: Synthesis of Conjugated Alkenyl(methyl)maleic Anhydride

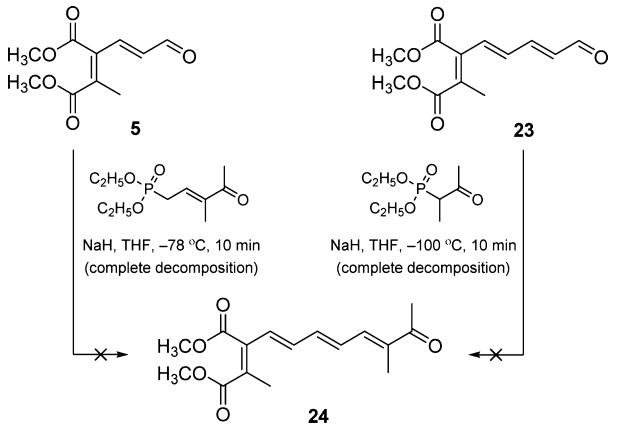


dx.doi.org/10.1021/jo402857r | J. Org. Chem. 2014, 79, 2538–2546

decomposition of the reaction mixture. However, the same Wittig reaction at −100 °C was successful and furnished triester **10** in 65% yield (2*Z*,4*E*,6*E*,8*E*:2*Z*,4*E*,6*E*,8*Z* = 9:1, by ^{1}H NMR), which was again transformed into geometrically pure dehomoitaconitin (**11a**) in 96% yield.

In an attempted synthesis of graphenone, we studied the reactions of aldehydes **5** and **23** with ketone-bearing Wittig reagents (Scheme 9). The HWE reaction of aldehyde **5** with

Scheme 9. Attempted Syntheses of Graphenone



diethyl (*E*)-(3-methyl-4-oxopent-2-en-1-yl)phosphonate[21] at −78 °C and the HWE reaction of aldehyde **23** with diethyl (3-oxobutan-2-yl)phosphonate at −100 °C unfortunately resulted in complete decomposition. In another plan, we decided to transform the dehomoitaconitin to the corresponding Weinreb amide and perform the Grignard reaction (Scheme 10). The *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC-HCl) induced coupling reaction of dehomoitaconitin (**11a**) with *N*,*O*-dimethylhydroxylamine hydrochloride in presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) was very clean, and TLC of the reaction mixture revealed the complete transformation of acid **11a** into the desired amide **25**. The silica gel column chromatographic purification of the labile amide **25** was not encouraging, and we could recover only one-third of the product accompanied by some contamination of decomposition residues. Hence, we did the complete characterization of the post-workup sample of the amide **25** without any purification. Like dehomoitaconitin, the anhydride moiety in product **25** was also in equilibrium with its dicarboxylic acid form in $CDCl_3$ solution (by ^{1}H NMR scanned after ∼24 h). As expected, the reaction of Weinreb amide **25** with Grignard reagent in THF was not chemoselective even at −78 °C and resulted in the formation of a complex mixture. However, the corresponding dilithium salt **26** in THF on treatment with a 10-fold excess of Grignard reagent at room temperature remained unreacted. The use of a THF/HMPA (3/1) solvent system for the reaction specified above also did not result in the formation of the desired product; instead, the reaction mixture underwent slow decomposition.

CONCLUSIONS

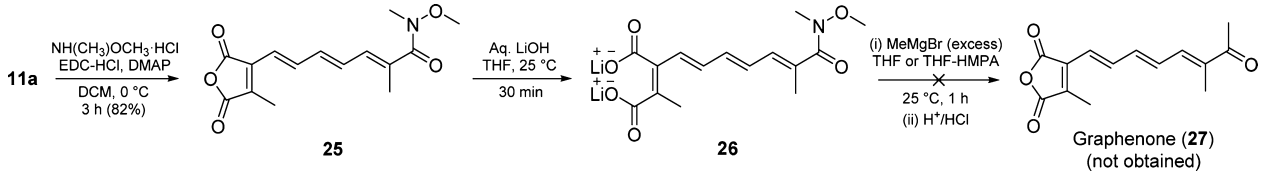
We have demonstrated the distinguishing conjugated 1,2-, 1,4-, and 1,6-elimination progressions in alkylidenesuccinates to design a unique approach to natural and unnatural alkenyl(methyl)maleic anhydrides. The described base-promoted 1,4-elimination of acetone with the cleavage of a cyclic ketal moiety and the well-ordered 1,6-elimination of a distantly placed mesylate are noteworthy from a basic chemistry point of view. The delocalization of formed carbanionic species in *α*,*β*-unsaturated and *α*,*β*,*γ*,*δ*-unsaturated carbonyl systems in the respective 1,4- and 1,6-elimination processes are thermodynamically favorable for stability reasons. We believe that these alkenyl(methyl)maleic anhydrides will exhibit potential RFTase inhibitory activity. We also believe that our present protocol will provide a practical approach to the analogues and congeners of target compounds for focused biological screenings.

EXPERIMENTAL SECTION

General Procedures. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200, 400, and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on a 200 MHz NMR spectrometer (50 MHz), a 400 MHz NMR spectrometer (100 MHz) and a 500 MHz NMR spectrometer (125 MHz). Mass spectra were taken on an MS-TOF mass spectrometer. HRMS (ESI) were taken on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60−120 and 200−400 mesh). Commercially available dimethyl maleate, tributylphosphine, (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde, NaHMDS, LiHMDS, *p*-TSA, *p*-toluenesulfonyl chloride, carbonyldiimidazole, thionyl chloride, methanesulfonyl chloride, IBX, NaH (60% dispersion in mineral oil), *N*,*O*-dimethylhydroxylamine hydrochloride, and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride were used.

Dimethyl (*S*,*E*)-2-((2,2-Dimethyl-1,3-dioxolan-4-yl)-methylene)succinate (2). To a stirred solution of dimethyl maleate (1.44 g, 10.00 mmol) and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (1.60 g, 12.00 mmol) in THF (10 mL) was added *n*-Bu_3P (3.73 mL, 15.00 mmol) in a dropwise fashion at 25 °C under an argon atmosphere. The reaction mixture was stirred for 12 h and concentrated in vacuo. The obtained residue was directly subjected to silica gel column chromatographic purification using a petroleum ether and ethyl acetate mixture (9/1) as an eluent to give a mixture of (*E*)- and (*Z*)-alkylidenesuccinate **2** as a thick oil (1.86 g, 72% yield). $[\alpha]^{25}_D = -19.3°$ (*c* 0.1, $CHCl_3$). Major *E* isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 1.40 (s, 3H), 1.45 (s, 3H), 3.35 (d, *J* = 16 Hz, 1H), 3.53 (d, *J* = 16 Hz, 1H), 3.68 (s, 3H), 3.70 (dd, *J* = 8 and 8 Hz, 1H), 3.76 (s, 3H), 4.16 (dd, *J* = 8 and 8 Hz, 1H), 4.78 (q, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ* 25.7, 26.5, 32.4, 52.2, 52.3, 68.7, 72.6, 110.1, 127.7, 141.8, 166.7, 170.7; ESIMS (*m*/*z*) 281 $[M + Na]^+$; HRMS (ESI) calcd for $C_{12}H_{18}O_6Na$ 281.0996, found 281.0984; IR ($CHCl_3$) ν_{max} 1742, 1720, 1657 cm^{-1}.

Scheme 10. Studies on Synthesis of Graphenone via Weinreb Amide



dx.doi.org/10.1021/jo402857r | J. Org. Chem. 2014, 79, 2538−2546

Dimethyl (*E*)-2-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-methylene)-3-methylsuccinate (3, Diastereomeric Mixture). To a stirred solution of alkylidenesuccinate **2** (516 mg, 2.00 mmol) in THF (7 mL) was added a solution of NaHMDS in THF (1 M, 2.60 mL, 2.60 mmol) in a dropwise manner at −78 °C under an argon atmosphere. The reaction mixture was stirred at same temperature for 30 min, and then MeI (0.15 mL, 2.40 mmol) was added. It was further stirred at −78 °C for 1.5 h and quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo, and the residue was dissolved in EtOAc (30 mL). The organic layer was washed with water and brine and dried over sodium sulfate. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using a petroleum ether and ethyl acetate mixture (9/1) as an eluent provided pure methyl alkylidenesuccinate **3** as a thick oil (397 mg, 73% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30−1.50 (m, 6H), 1.41 (s, 3H), 3.55−3.80 (m, 2H), 3.67 (s, 3H), 3.75 (br s, 3H), 4.07−4.23 (m, 1H), 4.83 (q, J = 8 Hz, 1H), 6.78 (dd, J = 8 and 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 16.6, 25.7, 26.5, 26.6, 38.0, 38.4, 52.0, 52.1, 68.8, 68.9, 72.3, 110.1, 110.2, 134.6, 134.7, 140.0, 140.1, 166.2, 173.4; ESIMS (m/z) 295 [M + Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_6Na$ 295.1152, found 295.1137; IR ($CHCl_3$) ν_{max} 1745, 1720, 1654 cm^{-1}.

Dimethyl 2-((*E*)-3-Hydroxyprop-1-en-1-yl)-3-methylmaleate (4). To a stirred solution of methyl alkylidenesuccinate **3** (380 mg, 1.40 mmol) in THF (5 mL) was added a solution of LiHMDS in THF (1 M, 2.80 mL, 2.80 mmol) in a dropwise mode at −78 °C under an argon atmosphere. The reaction mixture was stirred at same temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (25 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using a petroleum ether and ethyl acetate mixture (2/1) as an eluent yielded pure alcohol **4** as a thick oil (212 mg, 71% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.01 (s, 3H), 2.10−2.40 (br s, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 4.29 (d, J = 4 Hz, 2H), 6.03 (td, J = 16 and 4 Hz, 1H), 6.61 (td, J = 16 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 52.3, 52.4, 62.7, 122.6, 126.1, 138.4, 140.4, 167.5, 169.3; ESIMS (m/z) 237 [M + Na]$^+$; HRMS (ESI) calcd for $C_{10}H_{14}O_5Na$ 237.0733, found 237.0725; IR ($CHCl_3$) ν_{max} 3445, 1744, 1716, 1634, 1603 cm^{-1}.

Dimethyl 2-Methyl-3-((*E*)-3-oxoprop-1-en-1-yl)maleate (5). To a stirred solution of alcohol **4** (210 mg, 0.98 mmol) in ethyl acetate (4 mL) was added IBX (329 mg, 1.18 mmol), and the mixture was refluxed for 4 h. The reaction mixture was cooled to 25 °C, filtered through a pad of Celite, and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a petroleum ether and ethyl acetate mixture (3/1) as an eluent to furnish pure aldehyde **5** as a pale yellow solid (208 mg, ∼100% yield): mp 60−61 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 6.34 (dd, J = 16 and 8 Hz, 1H), 7.39 (d, J = 16 Hz, 1H), 9.70 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.8, 52.66, 52.73, 134.4, 136.2, 137.0, 142.2, 166.8, 167.2, 192.7; ESIMS (m/z) 235 [M + Na]$^+$; HRMS (ESI) calcd for $C_{10}H_{12}O_5Na$ 235.0577, found 235.0577; IR ($CHCl_3$) ν_{max} 2850, 1745, 1725, 1691, 1616 cm^{-1}.

1-Ethyl 5,6-Dimethyl (1*E*,3*E*,5*Z*)-Hepta-1,3,5-triene-1,5,6-tricarboxylate (6). To a stirred solution of aldehyde **5** (64 mg, 0.30 mmol) in DCM (3 mL) was added ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate (138 mg, 0.36 mmol) at 0 °C. The reaction mixture was stirred for 5 h and concentrated under vacuum. The obtained residue was purified by silica gel column chromatography using a petroleum ether and ethyl acetate mixture (4/1) as an eluent to afford a mixture of two geometric isomers of triester **6** as a yellow solid (40 mg, 82% yield): mp 50−51 °C. Major 1*E*,3*E*,5*Z* isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, J = 8 Hz, 3H), 2.08 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 4.22 (q, J = 8 Hz, 2H), 6.04 (d, J = 16 Hz, 1H), 6.47 (dd, J = 16 and 10 Hz, 1H), 6.81 (d, J = 16 Hz, 1H), 7.35 (dd, J = 16 and 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 14.2, 52.5, 52.6, 60.6, 125.1, 129.6, 131.9, 134.1, 140.0, 142.8, 166.4, 167.1, 168.5; ESIMS (m/z) 305 [M + Na]$^+$; HRMS (ESI) calcd for $C_{14}H_{18}O_6Na$ 305.0996, found 305.0994; IR ($CHCl_3$) ν_{max} 1738, 1729, 1710, 1618 cm^{-1}.

(2*E*,4*E*)-5-(4-Methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)penta-2,4-dienoic Acid (7). To a stirred solution of triester **6** (56 mg, 0.20 mmol) in THF (1 mL) was added 5% aqueous LiOH (1 mL) at 25 °C. The reaction mixture was stirred for 12 h and acidified by using 2 N HCl. The solvent was removed in vacuo, and the obtained residue was dissolved in EtOAc (15 mL). The organic layer was washed with water and brine and dried over sodium sulfate. It was concentrated in vacuo, and the obtained crude yellow solid was recrystallized from ethyl acetate to get pale yellow needles of anhydride **7** (38 mg, 93% yield): mp 191−192 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.25 (s, 3H), 6.36 (d, J = 15 Hz, 1H), 7.08 (d, J = 15 Hz, 1H), 7.46 (dd, J = 15 and 10 Hz, 1H), 7.64 (dd, J = 15 and 10 Hz, 1H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 9.7, 126.5, 127.8, 136.5, 138.5, 141.2, 144.0, 165.3, 166.7, 167.1; ESIMS (m/z) 231 [M + Na]$^+$; HRMS (ESI) calcd for $C_{10}H_8O_5Na$ 231.0264, found 231.0264; IR (Nujol) ν_{max} 2700−2500, 1768, 1755, 1716 cm^{-1}.

7-Ethyl 2,3-Dimethyl (2*Z*,4*E*,6*E*)-Nona-2,4,6-triene-2,3,7-tricarboxylate (8). To a stirred slurry of NaH (60% dispersion in mineral oil; 16 mg, 0.39 mmol) in THF (2 mL) was added ethyl 2-(diethoxyphosphoryl)butanoate (80 mg, 0.36 mmol) in THF (2 mL) in a dropwise manner at 0 °C under an argon atmosphere. After hydrogen evolution had ceased, the mixture was warmed to 25 °C and stirred for 5 min. The resulting mixture was cooled to 0 °C, and a solution of aldehyde **5** (64 mg, 0.30 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 45 min and then quenched with saturated aqueous NH_4Cl. The solvent was removed under vacuum, and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with water and brine and dried over sodium sulfate. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using a petroleum ether and ethyl acetate mixture (4/1) as an eluent afforded a mixture of two geometric isomers of triester **8** as a yellow solid (73 mg, 78% yield): mp 56−57 °C. Major 2*Z*,4*E*,6*E* isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, J = 8 Hz, 3H), 1.31 (t, J = 8 Hz, 3H), 2.07 (s, 3H), 2.43 (q, J = 8 Hz, 2H), 3.77 (s, 3H), 3.88 (s, 3H), 4.23 (q, J = 8 Hz, 2H), 6.66 (dd, J = 16 and 12 Hz, 1H), 6.78 (d, J = 16 Hz, 1H), 7.21 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 14.2, 14.3, 20.7, 52.45, 52.47, 60.8, 128.5, 130.8, 131.5, 136.2, 137.9, 140.6, 167.2, 167.4, 168.7; ESIMS (m/z) 333 [M + Na]$^+$; HRMS (ESI) calcd for $C_{16}H_{22}O_6Na$ 333.1309, found 333.1304; IR ($CHCl_3$) ν_{max} 1736, 1709, 1616 cm^{-1}.

(2*E*,4*E*)-2-Ethyl-5-(4-methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)penta-2,4-dienoic Acid (2,3-Didehydrotelfairic Anhydride, 9). The title compound was obtained from triester **8** (62 mg, 0.20 mmol) and 5% aqueous LiOH (1 mL) using the same procedure as described for compound **7**. The product was recrystallized from ethyl acetate to provide pale yellow needles of natural product **9** (44 mg, 93% yield): mp 199−201 °C (lit.[7] mp 203−205 °C); ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.11 (t, J = 8 Hz, 3H), 2.25 (s, 3H), 2.57 (q, J = 8 Hz, 2H), 7.03 (d, J = 16 Hz, 1H), 7.34 (d, J = 12 Hz, 1H), 7.85 (dd, J = 12 and 16 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 9.6 14.7, 21.4, 125.6, 135.8, 136.9, 137.2, 140.3, 140.7, 165.5, 166.8, 168.4; ESIMS (m/z) 259 [M + Na]$^+$; IR (Nujol) ν_{max} 2700−2500, 1768, 1756, 1713 cm^{-1}.

Trimethyl (2*Z*,4*E*,6*E*,8*E*)-Deca-2,4,6,8-tetraene-2,3,9-tricarboxylate (10). *Method A.* To a stirred slurry of NaH (60% dispersion in mineral oil; 16 mg, 0.39 mmol) in THF (2 mL) was added methyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (79 mg, 0.36 mmol) in THF (2 mL) in a dropwise manner at −20 °C under an argon atmosphere. After the evolution of hydrogen had ceased, the reaction mixture was warmed to 0 °C and stirred for 5 min. The resulting mixture was cooled to −20 °C, and a solution of aldehyde **5** (64 mg, 0.30 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 30 min and quenched with saturated aqueous NH_4Cl. The solvent was removed in vacuo, and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with water and brine and dried over sodium sulfate. It was

dx.doi.org/10.1021/jo402857r | J. Org. Chem. 2014, 79, 2538−2546

concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using a petroleum ether and ethyl acetate mixture (6/1) as an eluent to yield a mixture of two geometric isomers of triester **10** as a yellow solid (71 mg, 76% yield).

Method B. To a stirred slurry of NaH (60% dispersion in mineral oil; 11 mg, 0.27 mmol) in THF (2 mL) was added ethyl 2-(diethoxyphosphoryl)propanoate (57 mg, 0.25 mmol) in THF (2 mL) in a dropwise manner at −20 °C under an argon atmosphere. After the evolution of hydrogen had ceased, the reaction mixture was warmed to 0 °C and stirred for 5 min. The resulting mixture was cooled to −100 °C, and a solution of aldehyde **23** (50 mg, 0.21 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 20 min and quenched with saturated aqueous NH_4Cl at −78 °C. The workup specified above followed by purification gave a mixture of two geometric isomers of product **10** (42 mg, 65% yield): mp 98−100 °C. Major 2*Z*,4*E*,6*E*,8*E* isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.00 (s, 3H), 2.07 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 6.35−6.80 (m, 4H), 7.25 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.0, 13.8, 52.0, 52.4, 52.6, 126.9, 127.8, 129.4, 132.1, 136.8, 137.4, 137.9, 141.3, 167.2, 168.5, 169.1; ESIMS (m/z) 331 $[M + Na]^+$; HRMS (ESI) calcd for $C_{16}H_{20}O_6Na$ 331.1152, found 331.1150; IR ($CHCl_3$) ν_{max} 1740, 1732, 1709, 1617 cm^{-1}.

(2*E*,4*E*,6*E*)-2-Methyl-7-(4-methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)hepta-2,4,6-trienoic Acid (Dehomoitaconitin, 11a). The title compound was obtained from triester **10** (60 mg, 0.20 mmol) and 5% aqueous LiOH (1 mL) using the same procedure as described for compound **7**. The crude product was recrystallized from ethyl acetate to furnish pale yellow needles of anhydride **11a** (46 mg, 96% yield): mp 220−222 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.04 (s, 3H), 2.20 (s, 3H), 6.79 (d, J = 15 Hz, 1H), 6.86 (dd, J = 15 and 15 Hz, 1H), 7.13 (t, J = 15 Hz, 1H), 7.31 (d, J = 10 Hz, 1H), 7.69 (dd, J = 15 and 10 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 9.8, 13.3, 122.5, 131.9, 135.4, 137.5, 138.1, 138.5, 139.3, 141.6, 165.8, 167.1, 169.2; ESIMS (m/z) 271 $[M + Na]^+$; HRMS (ESI) calcd for $C_{13}H_{12}O_5Na$ 271.0577, found 271.0574; IR (Nujol) ν_{max} 2700−2500, 1767, 1754, 1715 cm^{-1}.

Dimethyl (*E*)-2-((*E*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-allylidene)succinate (12). The title compound was obtained from dimethyl maleate (432 mg, 3.00 mmol), (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (562 mg, 3.60 mmol), and *n*-Bu_3P (1.12 mL, 4.50 mmol) in THF (3 mL) using the same procedure as described for compound **2** as a thick oil (mixture of two geometric isomers) (605 mg, 71% yield): $[\alpha]^{25}_D$ = = +3.4° (c 0.1, $CHCl_3$). Major 2*E*,3*E* isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.45 (s, 3H), 3.47 (s, 2H), 3.58−3.73 (m, 1H), 3.69 (s, 3H), 3.78 (s, 3H), 4.16 (dd, J = 8 and 6 Hz, 1H), 4.65 (q, J = 6 Hz, 1H), 6.12 (dd, J = 16 and 8 Hz, 1H), 6.56 (dd, J = 14 and 12 Hz, 1H), 7.35 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.7, 26.5, 32.3, 52.11, 52.14, 69.2, 76.1, 109.9, 125.0, 126.6, 139.7, 140.1, 167.4, 170.8; ESIMS (m/z) 307 $[M + Na]^+$; HRMS (ESI) calcd for $C_{14}H_{20}O_6Na$ 307.1152, found 307.1143; IR ($CHCl_3$) ν_{max} 1739, 1715, 1646, 1615 cm^{-1}.

Dimethyl (*E*)-2-((*E*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-allylidene)-3-methylsuccinate (13, Diastereomeric Mixture). The title compound was obtained from alkylidenesuccinate **12** (570 mg, 2.00 mmol), NaHMDS in THF (1 M, 2.60 mL, 2.60 mmol), and MeI (0.15 mL, 2.40 mmol) using the same procedure as described for compound **3** as a thick oil (448 mg, 75% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (d, J = 8 Hz, 3H), 1.41 (s, 3H), 1.45 (s, 3H), 3.58−3.80 (m, 2H), 3.66 (s, 3H), 3.75 (s, 3H), 4.17 (dd, J = 10 and 8 Hz, 1H), 4.65 (q, J = 6 Hz, 1H), 6.11 (dd, J = 16 and 8 Hz, 1H), 6.59 (dd, J = 16 and 12 Hz, 1H), 7.25 (d, J = 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1, 25.7, 26.5, 37.9, 51.9, 52.0, 69.2, 76.0, 76.1, 109.9, 126.1, 126.2, 131.8, 131.9, 138.07, 138.14, 140.0, 140.1, 166.91, 166.94, 173.7; ESIMS (m/z) 321 $[M + Na]^+$; HRMS (ESI) calcd for $C_{15}H_{22}O_6Na$ 321.1309, found 321.1309; IR ($CHCl_3$) ν_{max} 1729, 1716, 1651 cm^{-1}.

Dimethyl (*E*)-2-((*S*,*E*)-4,5-Dihydroxypent-2-en-1-ylidene)-3-methylsuccinate (14, Diastereomeric Mixture). To a stirred solution of compound **13** (400 mg, 1.34 mmol) in MeOH (8 mL) was added *p*-TSA hydrate (26 mg, 10 mol %) at 25 °C. The reaction mixture was stirred for 8 h, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (30 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine. It was dried over sodium sulfate and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a petroleum ether and ethyl acetate mixture (1/1) as an eluent to give pure diol **14** as a thick oil (305 mg, 88% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (d, J = 8 Hz, 3H), 3.43−3.60 (m, 1H), 3.60−3.83 (m, 2H), 3.65 (s, 3H), 3.74 (s, 3H), 4.30−4.45 (m, 1H), 6.14 (dd, J = 15 and 6 Hz, 1H), 6.64 (dd, J = 14 and 12 Hz, 1H), 7.24 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 37.9, 52.0, 52.1, 66.0, 72.4, 125.1, 131.2, 138.6, 141.5, 167.1, 174.2; ESIMS (m/z) 281 $[M + Na]^+$; HRMS (ESI) calcd for $C_{12}H_{18}O_6Na$ 281.0996, found 281.0990; IR ($CHCl_3$) ν_{max} 3453, 1733, 1715, 1654 cm^{-1}.

Dimethyl (*E*)-2-((*S*,*E*)-4-Hydroxy-5-(tosyloxy)pent-2-en-1-ylidene)-3-methylsuccinate (15, Diastereomeric Mixture). To a solution of compound **14** (50 mg, 0.19 mmol) in DCM (5 mL) was added dibutyltin oxide (10 mg, 20 mol %) at 0 °C under an argon atmosphere, and the reaction mixture was stirred for 30 min. To the above reaction mixture was added triethylamine (0.026 mL, 0.19 mmol) followed by tosyl chloride (36 mg, 0.19 mmol), and it was stirred at 25 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (15 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using a petroleum ether and ethyl acetate mixture (2/1) as an eluent furnished pure product **15** as a thick oil (80 mg, 77% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36 (d, J = 8 Hz, 3H), 2.47 (s, 3H), 3.66 (s, 3H), 3.68−3.80 (m, 1H), 3.76 (s, 3H), 3.95 (ddd, J = 10, 6, and 2 Hz, 1H), 4.11 (dd, J = 10 and 4 Hz, 1H), 4.50−4.63 (m, 1H), 6.00 (dd, J = 14 and 6 Hz, 1H), 6.65 (dd, J = 14 and 12 Hz, 1H), 7.19 (d, J = 10 Hz, 1H), 7.37 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0, 21.6, 37.8, 51.9, 52.1, 69.4, 72.4, 126.1, 127.9, 129.9, 131.9, 132.3, 138.0, 138.7, 145.2, 166.9, 173.8; ESIMS (m/z) 435 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{25}O_8S$ 413.1265, found 413.1280; IR ($CHCl_3$) ν_{max} 3436, 1733, 1711, 1598 cm^{-1}.

Dimethyl (*E*)-2-Methyl-3-((*E*)-3-((*S*)-oxiran-2-yl)allylidene)-succinate (16, Diastereomeric Mixture). To a stirred slurry of NaH (60% dispersion in mineral oil; 8 mg, 0.20 mmol) in THF (1 mL) was added compound **15** (70 mg, 0.17 mmol) in THF (2 mL) in a dropwise manner at 0 °C under an argon atmosphere. After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and solvent was removed in vacuo. The residue was dissolved in EtOAc (20 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using a petroleum ether and ethyl acetate mixture (4/1) as an eluent yielded epoxide **16** as a thick oil (41 mg, 71% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, J = 8 Hz, 3H), 2.73 (dd, J = 6 and 4 Hz, 1H), 3.07 (t, J = 6 Hz, 1H), 3.40−3.51 (m, 1H), 3.67 (s, 3H), 3.70−3.85 (m, 1H), 3.76 (s, 3H), 5.85 (ddd, J = 14, 8, and 4 Hz, 1H), 6.71 (dd, J = 16 and 12 Hz, 1H), 7.25 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 16.2, 37.91, 37.93, 49.5, 51.55, 51.63, 52.0, 52.1, 127.6, 127.8, 131.69, 131.72, 137.75, 137.78, 140.0, 140.1, 167.0, 173.8; ESIMS (m/z) 263 $[M + Na]^+$; HRMS (ESI) calcd for $C_{12}H_{17}O_5$ 241.1071, found 241.1070; IR ($CHCl_3$) ν_{max} 1733, 1714, 1622 cm^{-1}.

Dimethyl (*E*)-2-Methyl-3-((*E*)-3-((*S*)-2-oxo-1,3-dioxolan-4-yl)-allylidene)succinate (18, Diastereomeric Mixture). To a stirred solution of compound **14** (50 mg, 0.19 mmol) in DCM (2 mL) was added carbonyldiimiazole (37 mg, 0.23 mmol) at 25 °C under an argon atmosphere. The reaction mixture was stirred for 4 h, and the solvent was removed in vacuo. The residue was dissolved in EtOAc (15 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. The organic layer was concentrated in vacuo, and the obtained residue was purified by silica gel column chromatography using a petroleum ether and ethyl acetate mixture (2/1) as an eluent to provide carbonate **18** as a thick oil (49 mg, 89%

dx.doi.org/10.1021/jo402857r | J. Org. Chem. 2014, 79, 2538−2546

yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (dd, J = 6 and 2 Hz, 3H), 3.67 (s, 3H), 3.68−3.82 (m, 1H), 3.78 (s, 3H), 4.20 (dd, J = 8 and 8 Hz, 1H), 4.66 (t, J = 8 Hz, 1H), 5.28 (q, J = 8 Hz, 1H), 6.11 (dd, J = 16 and 6 Hz, 1H), 6.71 (dd, J = 14 and 12 Hz, 1H), 7.24 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1, 16.2, 37.97, 38.03, 52.19, 52.22, 68.9, 76.1, 76.3, 128.9, 129.1, 134.2, 134.5, 134.6, 136.3, 136.4, 154.3, 166.49, 166.52, 173.29, 173.34; ESIMS (m/z) 307 [M + Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{17}O_7$ 285.0969, found 285.0967; IR ($CHCl_3$) ν_{max} 1805, 1733, 1646, 1610 cm^{-1}.

Dimethyl (*E*)-2-Methyl-3-((*E*)-3-((4*S*)-2-oxido-1,3,2-dioxathiolan-4-yl)allylidene)succinate (19, Diastereomeric Mixture). To a stirred solution of compound **14** (50 mg, 0.19 mmol) in DCM (2 mL) were added triethylamine (0.053 mL, 0.38 mmol) followed by thionyl chloride (0.017 mL, 0.28 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 30 min, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (15 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. Concentration of the organic layer in vacuo and silica gel column chromatographic purification of the obtained residue using a petroleum ether and ethyl acetate mixture (2/1) as an eluent gave pure sulfite **19** as a thick oil (49 mg, 83% yield: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, J = 6 Hz, 3H), 3.67 (s, 3H), 3.68−3.80 (m, 1H), 3.77 (s, 3H), 4.08 (dd, J = 10 and 6 Hz, 0.50H), 4.42 (t, J = 10 Hz, 0.50H), 4.62 (dd, J = 10 and 6 Hz, 0.50H), 4.81 (dd, J = 8 and 6 Hz, 0.50H), 5.03 (q, J = 8 Hz, 0.50H), 5.51 (q, J = 6 Hz, 0.50H), 6.02 (dd, J = 16 and 8 Hz, 0.50H), 6.20 (dd, J = 16 and 8 Hz, 0.50H), 6.69 (dd, J = 16 and 12 Hz, 1H), 7.24 (dd, J = 12 and 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1, 37.96, 37.99, 52.1, 69.5, 71.2, 79.3, 79.4, 82.9, 83.0, 129.1, 129.3, 129.88, 129.93, 133.6, 133.9, 133.98, 134.04, 134.1, 134.8, 134.9, 136.6, 136.65, 136.69, 166.6, 173.3, 173.39, 173.43; ESIMS (m/z) 327 [M + Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{16}O_7NaS$ 327.0509, found 327.0507; IR ($CHCl_3$) ν_{max} 1714, 1646 cm^{-1}.

Dimethyl (*E*)-2-Methyl-3-((*E*)-4-oxopent-2-en-1-ylidene)-succinate (20). To a stirred solution of compound **18**/**19** (40/40 mg, 0.14/0.13 mmol) in THF (4 mL) was added a solution of LiHMDS in THF (1 M, 0.28/0.26 mL, 0.28/0.26 mmol) in a dropwise fashion at −78 °C under an argon atmosphere. The reaction mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the solvent was removed in vacuo. The residue was dissolved in EtOAc (15 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. The concentration of the organic layer followed by silica gel column chromatography of the resulting residue using a petroleum ether and ethyl acetate mixture (4/1) as an eluent furnished pure ketone **20** as a thick oil (28/23 mg, 82/73% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (d, J = 6 Hz, 3H), 2.34 (s, 3H), 3.68 (s, 3H), 3.80 (s, 3H), 3.86 (q, J = 8 Hz, 1H), 6.48 (d, J = 14 Hz, 1H), 7.20−7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3, 28.2, 38.3, 52.2, 52.3, 134.9, 136.2, 136.5, 138.7, 166.2, 173.1, 197.7; ESIMS (m/z) 263 [M + Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{17}O_5$ 241.1071, found 241.1072; IR ($CHCl_3$) ν_{max} 1740, 1720, 1674, 1625 cm^{-1}.

Dimethyl (*E*)-2-((*S*,*E*)-4-Hydroxy-5-((methylsulfonyl)oxy)-pent-2-en-1-ylidene)-3-methylsuccinate (21, Diastereomeric Mixture) and Dimethyl (*E*)-2-((*S*,*E*)-5-Hydroxy-4-((methylsulfonyl)oxy)pent-2-en-1-ylidene)-3-methylsuccinate (22, Diastereomeric Mixture). To a stirred solution of compound **14** (180 mg, 0.70 mmol) in DCM (10 mL) were added triethylamine (0.127 mL, 0.91 mmol) followed by mesyl chloride (0.065 mL, 0.84 mmol) and DMAP (4 mg, 5 mol %) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 2 h and quenched with saturated aqueous NH_4Cl. Solvent was removed in vacuo, and the residue was dissolved in EtOAc (25 mL). The organic layer was washed with water and brine and dried over sodium sulfate. Concentration of the organic layer in vacuo gave a mixture of mesylates **21** and **22** in a 1/1 ratio. The obtained mixture of primary and secondary mesylates was separated by silica gel column chromatography using a petroleum ether and ethyl acetate mixture (7/3) as an eluent to afford pure products as thick oils (85/86 mg, 73% yield).

21: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38 (d, J = 8 Hz, 3H), 2.02 (br s, 1H), 3.09 (s, 3H), 3.67 (s, 3H), 3.70−3.85 (m, 1H), 3.76 (s, 3H), 4.16 (dd, J = 12 and 8 Hz, 1H), 4.32 (dd, J = 12 and 4 Hz, 1H), (4.57−4.70 m, 1H), 6.11 (dd, J = 16 and 6 Hz, 1H), 6.72 (dd, J = 12 and 12 Hz, 1H), 7.25 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1, 37.7, 37.9, 52.0, 52.2, 69.8, 72.0, 126.5, 132.4, 137.8, 138.3, 166.9, 173.8; ESIMS (m/z) 359 [M + Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_8NaS$ 359.0771, found 359.0768; IR ($CHCl_3$) ν_{max} 3445, 1728 cm^{-1}.

22: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (d, J = 6 Hz, 3H), 1.77 (br s, 1H), 3.09 (s, 3H), 3.67 (s, 3H), 3.70−3.80 (m, 1H), 3.77 (s, 3H), 4.30−4.47 (m, 2H), 4.73 (q, J = 8 Hz, 1H), 6.11 (dd, J = 14 and 8 Hz, 1H), 6.67 (dd, J = 16 and 12 Hz, 1H), 7.23 (d, J = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 31.5, 37.9, 38.0, 52.1, 52.2, 56.99, 57.02, 70.27, 70.33, 128.88, 128.91, 133.9, 134.0, 135.8, 136.8, 166.6, 173.5; ESIMS (m/z) 359 [M + Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{20}O_8NaS$ 359.0771, found 359.0768; IR ($CHCl_3$) ν_{max} 3440, 1729 cm^{-1}.

Dimethyl 2-((1*E*,3*E*)-5-Hydroxypenta-1,3-dien-1-yl)-3-methylmaleate (17). To a stirred slurry of NaH (60% dispersion in mineral oil; 27 mg, 0.68 mmol) in DMF (2 mL) was added a mixture of compounds **21** and **22** (150 mg, 0.45 mmol) in DMF (2 mL) in a dropwise mode at 0 °C under an argon atmosphere. After it was stirred for 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and the solvent was removed under vacuum. The residue was dissolved in EtOAc (25 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. The organic layer was concentrated in vacuo, and the obtained residue was purified by silica gel column chromatography using a petroleum ether and ethyl acetate mixture (2/1) as an eluent to provide alcohol **17** as a thick oil (69 mg, 64% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85 (br s, 1H), 2.02 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.25 (d, J = 6 Hz, 2H), 5.95−6.10 (m, 1H), 6.30−6.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 52.3, 52.4, 62.8, 125.2, 125.6, 129.8, 136.8, 137.6, 141.5, 167.3, 169.3; ESIMS (m/z) 263 [M + Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{17}O_5$ 241.1071, found 241.1070; IR ($CHCl_3$) ν_{max} 3502, 1756, 1722, 1634 cm^{-1}.

Dimethyl 2-Methyl-3-((1*E*,3*E*)-5-oxopenta-1,3-dien-1-yl)-maleate (23). The title compound was obtained from alcohol **17** (60 mg, 0.25 mmol) and IBX (84 mg, 0.30 mmol) as a thick oil using the same procedure as described for compound **5** (59 mg, ∼100% yield): mp 89−91 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 6.29 (dd, J = 14 and 8 Hz, 1H), 6.61 (dd, J = 16 and 10 Hz, 1H), 6.94 (d, J = 16 Hz, 1H), 7.21 (dd, J = 16 and 10 Hz, 1H), 9.64 (d, J = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 52.6, 52.7, 131.2, 133.5, 133.8, 134.2, 139.5, 149.6, 167.0, 168.2, 193.1; ESIMS (m/z) 261 [M + Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{14}O_5Na$ 261.0733, found 261.0731; IR ($CHCl_3$) ν_{max} 3445, 2854, 1734, 1674, 1627 cm^{-1}.

(2*E*,4*E*,6*E*)-*N*-Methoxy-*N*,2-dimethyl-7-(4-methyl-2,5-dioxo-2,5-dihydrofuran-3-yl)hepta-2,4,6-trienamide (25). To a stirred solution of acid **11a** (50 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) were added *N*,*O*-dimethylhydoxylamine hydrochloride (24 mg, 0.24 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (77 mg, 0.40 mmol), and DMAP (3 mg, 10 mol %) at 0 °C under an argon atmosphere. The reaction mixture was warmed to 25 °C and further stirred for 3 h. The reaction mixture was concentrated in vacuo, and the obtained residue was dissolved in EtOAc (20 mL). The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated in vacuo to provide the product **25** as a bright yellow gummy solid (48 mg, 82% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.08 (s, 3H), 2.15 (s, 3H), 3.26 (s, 3H), 3.65 (s, 3H), 6.40 (d, J = 16 Hz, 1H), 6.40−6.60 (m, 2H), 6.88 (dd, J = 14 and 12 Hz, 1H), 7.68 (dd, J = 16 and 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.4, 14.8, 33.3, 61.2, 119.3, 131.2, 134.8, 135.2, 135.5, 136.0, 137.0, 141.9, 164.4, 166.0, 171.8; HRMS (ESI) calcd for $C_{15}H_{18}O_5N$ 292.1179, found 292.1179; IR ($CHCl_3$) ν_{max} 1761, 1635 cm^{-1}.

dx.doi.org/10.1021/jo402857r | J. Org. Chem. 2014, 79, 2538−2546

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR, ^{13}C NMR and DEPT spectra of compounds **2**−**10**, **11a**, **12**−**23**, and **25** and a table giving a comparison of ^{1}H and ^{13}C NMR data between natural and synthetic 2,3-didehydrotelfairic anhydride (**9**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Dr. V. Balasubramaniyan, Nashik, MS, India, on the occasion of his 81st birthday. P.S.D. thanks the CSIR, New Delhi, India, for the award of a research fellowship. N.P.A. thanks the Department of Science and Technology, New Delhi, India, for financial support.

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