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Concise synthesis and revision of the proposed biogenesis of helicascolides

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ABSTRACT

A concise synthesis of helicascolides A, B and C was achieved in three to five steps from commercially available materials. The key transformations of the synthesis include an Evans-Metternich *anti*-aldol reaction of the known β-keto imide **10** and strategic base-mediated one-pot cyclization/alkylation. Based on the new chemical evidence of ring-opening reaction of β-keto ester under biocompatible basic conditions, Krohn's proposal for the biosynthetic relationship between helicascolide A (**1**) and a naturally co-existing acyclic dienone **4** was suggested in a reverse manner.

Marine microorganisms have been intensely exploited for their novel bioactive secondary metabolites from diverse biosynthetic origins.[1] Helicascolides A (**1**) and B (**2**) (Fig. 1) were first isolated by Gloer and co-workers from the marine fungus *Helicascus kanaloanus* (ATCC 18591) in 1989.[2] Recently, Tarman and co-workers reported the characterization of structurally related helicascolide C (**3**) from an Indonesian marine algicolous strain *Gracilaria* sp. SGR-1.[3] Interestingly, only helicascolide C (**3**) shows a notable ability to inhibit the growth of *Cladosporium cucumerinum*, a pathogenic plant fungus that affects cucumbers. In 2006, Krohn and co-workers[4] isolated the biologically active linear metabolite (4*E*,6*E*)-2,4,6-trimethylocta-4,6-dien-3-one (**4**) along with helicascolide A (**1**) from the endophytic fungus *Nodulisporium* sp. From a structural perspective, helicascolides (**1**–**3**) belong to a small family of partially dehydrated tetraketides that are characterized by a highly congested δ-lactone ring system with *gem*-dimethyl substitution at the C2 position.

With the ongoing interest in the development of bioinspired synthetic strategies for the efficient syntheses of bioactive polyketides,[5] the molecular architecture of helicascolides captured our interest, since the specific scaffold is found in various natural products or natural product-like synthetic intermediates (**5**–**7** in Fig. 1).[6,7] The first total synthesis of **1** and **3**, disclosed by Krishna and co-workers,[8] featured a one-pot acid-catalyzed acetonide removal and subsequent lactonization. The Yadav group[9] achieved a concise total synthesis of **1**–**3** by employing a similar ring-forming strategy and utilizing iterative aldolization to access the precursor in a more efficient manner.[10] In 2016, Breit and co-workers[11] also accomplished the total syntheses of **1**–**3** by intramolecular Rh-catalyzed diastereoselective additions of chiral ω-allenyl carboxylic acids. Herein, we present a short synthesis of all the representatives of the helicascolide family, which were assembled with the longest linear sequences ranging from three to five steps.

Retrosynthetically, we envisioned that structurally simpler helicascolide C (**3**), for which the most oxidized carbon is C3, could serve as the primary target and a branching intermediate to access the other congeners of the family via late-stage stereoselective reduction of the C3-ketone (Scheme 1). By taking advantage of this distinctly different tactic, methylation at C2 of cyclic β-keto ester enolate **8** should be feasible. This synthetic strategy is largely simulating a possible biosynthetic pathway that involves chain elongation and methylation initiated by SAM (*S*-adenosyl methionine). Anionic intermediate **8** should be accessible from the cyclization of aldolate anion **9**, in which the entire tetraketide backbone could be derived from the reaction of known Evans' dipropionate synthon **10**[12] with tiglic aldehyde. Integral to this approach was the dramatic increase in the kinetic acidity of the C2 position of **8**, which was a result of the enolization favoring a cyclized product conformation in which better orbital overlap between σ-C2-H and π*-C3-O could be realized[13].

Chiral β-keto imide **10** was readily prepared in a two-step protocol (Scheme 2) that included an Evans *syn*-aldol reaction

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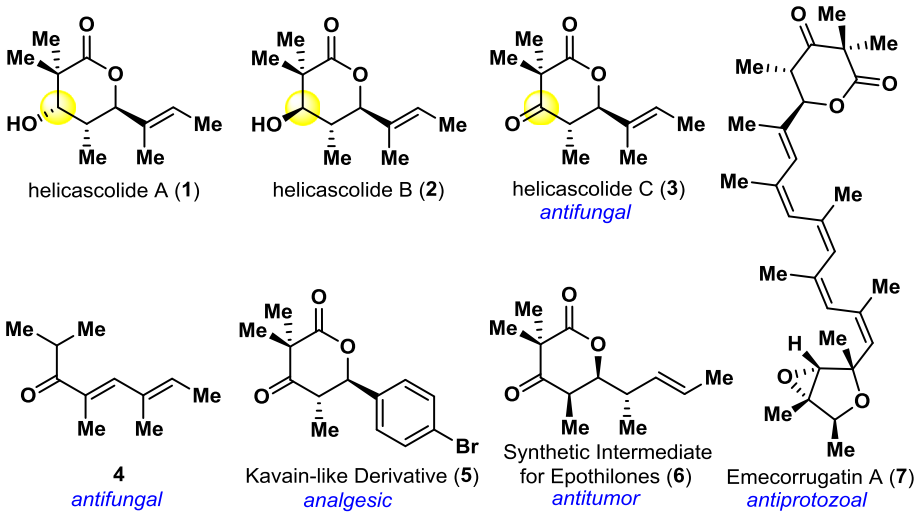
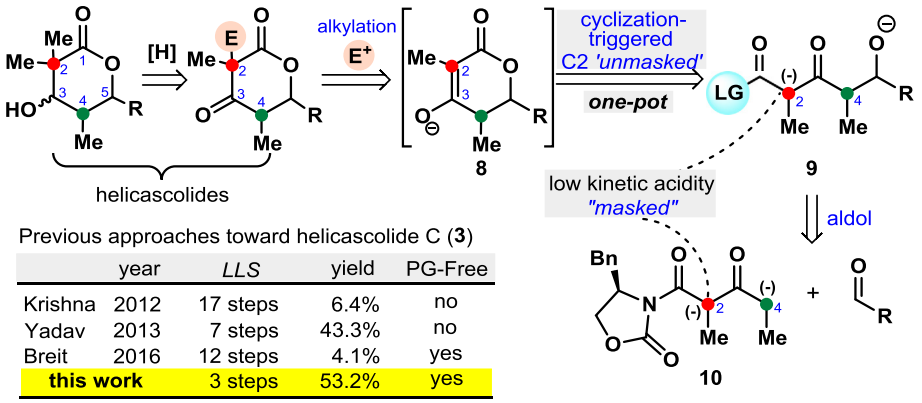


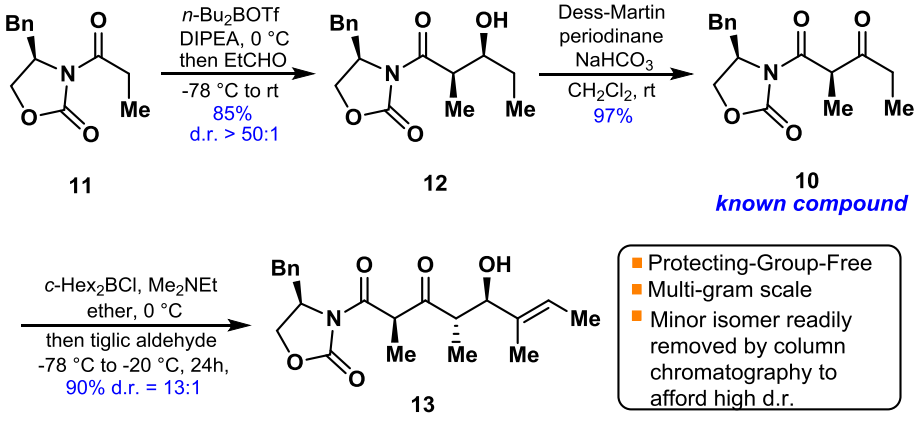
Fig. 1. Helicascolides and structurally related compounds.



Previous approaches toward helicascolide C (**3**)

	year	*LLS*	yield	PG-Free
Krishna	2012	17 steps	6.4%	no
Yadav	2013	7 steps	43.3%	no
Breit	2016	12 steps	4.1%	yes
this work		3 steps	53.2%	yes

Scheme 1. Retrosynthetic analysis of the helicascolides. [H] = reduction; R = substituent; LG = leaving group; LLS = the longest linear steps; PG = protecting group.

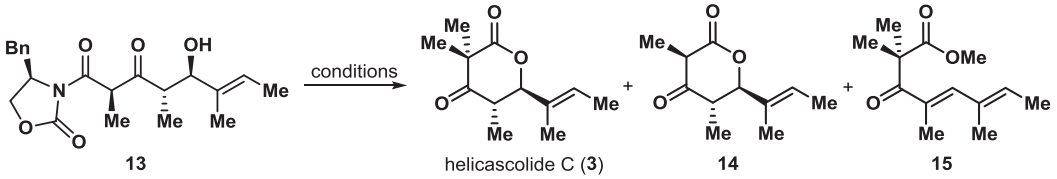


Scheme 2. Synthesis of compound **13**.

between commercially available *N*-acyloxazolidinone **11** and propanal followed by Dess-Martin oxidation of corresponding alcohol **12**. Addition of the (*E*)-boron enolate pre-formed from **10** to tiglic aldehyde provided two *anti*-aldol adducts in 90% combined yield with a diastereomeric ratio (d.r.) of 13:1.[14] A second purification using flash column chromatography further enriched the d.r. up to 30:1.

With several grams of the requisite acyclic tetraketide **13** in hand, we were in a position to test the feasibility of the crucial cyclization/alkylation cascade (conversion of **9** to **3** shown in Scheme 1). Initially, the cyclization reaction was carried out under conventional conditions[15] for analogous substrates bearing a C3-hydroxyl group; however, extensive decomposition was observed (entries 1 and 2 in Table 1). Next, we found that treatment of **13**

Table 1
Optimization for "one-pot" cyclization/alkylation of **13**.[a]



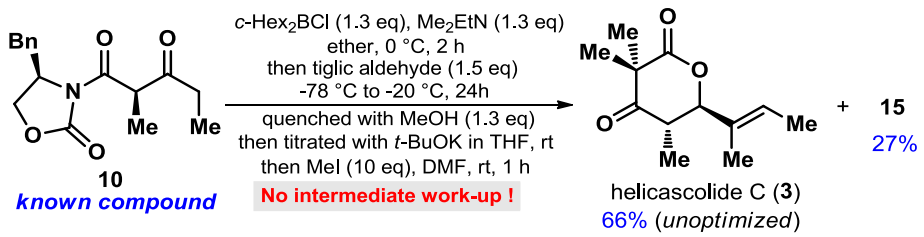
Entry	Conditions	Temperature	Reaction time	Yield (%)[b]		
				3	**14**	**15**
1[c]	LiOOH (2.0 equiv), THF/H_2O	0 °C	2 h	–	trace[c]	–
2[c]	DBU (1.0 equiv), DCM	0 °C	2 h	–	trace[c]	–
3[c]	^{t}BuOK, toluene	rt	1 min	–	80	–
4	^{t}BuOK, then MeI, toluene	rt	10 min	0	78	0
5	^{t}BuOK, then MeI, toluene	55 °C	10 min	0	72	0
6	^{t}BuOK, then MeI, benzene	55 °C	10 min	0	75	0
7	^{t}BuOK, then MeI, DMSO	55 °C	10 min	90	trace[d]	4
8	^{t}BuOK, then MeI, DMF	55 °C	10 min	88	trace[d]	4
9	^{t}BuOK, then MeI, DMF	rt	10 min	90	trace[d]	2
10	^{t}BuOK, then MeI, THF	rt	10 min	92	trace[d]	0
11	MeI, then ^{t}BuOK, THF	rt	10 min	67	11	0

[Note]: (a) *t*-BuOK (1.05 equiv) and MeI (2.0 equiv) were utilized unless otherwise noted. (b) Isolated yield. (c) For entries 1–3, the reaction mixture was analyzed by ^{1}H NMR (400 MHz, $CDCl_3$) after a simple work-up. (d) Less than 2% yield.

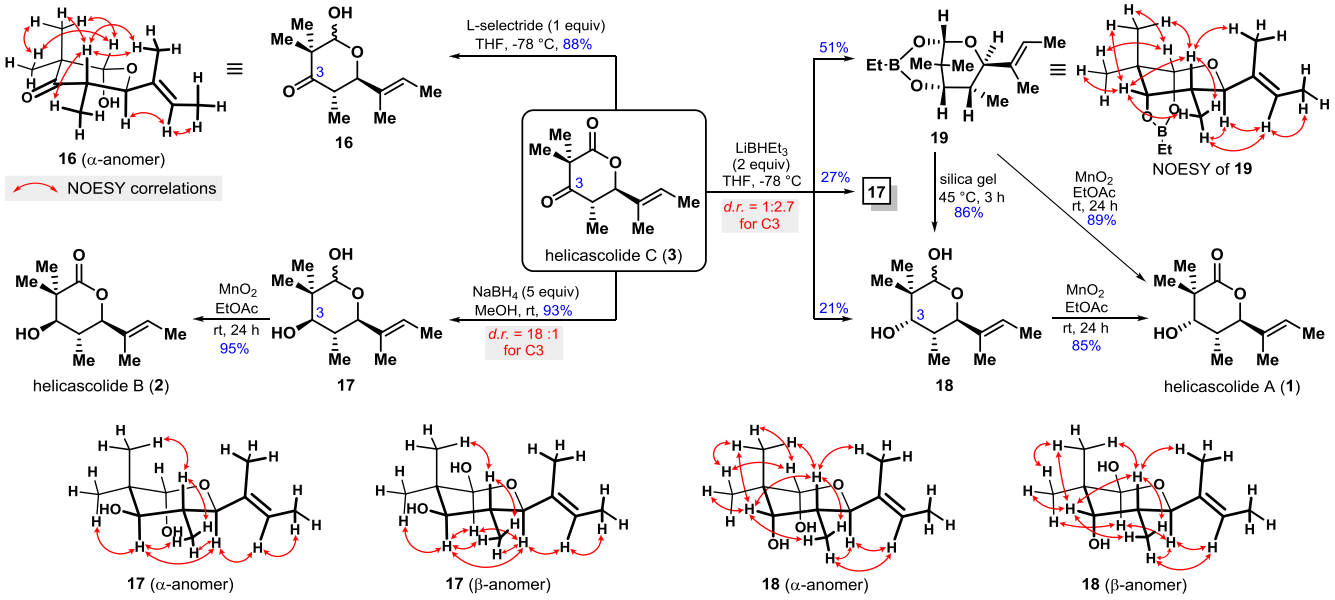
with 1.05 equiv of *t*-BuOK in toluene at room temperature resulted in rapid formation of β-keto lactone **14**, which was isolated as an unstable colorless oil (entry 3). To our surprise, introduction of the methyl group by MeI under the same conditions did not provide the desired alkylation product helicascolide C (**3**) in an appreciable yield, even at elevated temperature (entries 4 and 5). Interestingly, when more polar aprotic solvents, such as DMF and DMSO, were used, C2-alkylation exclusively occurred, and UV-inactive material **3** was generated in excellent yield (entries 7 and 8). Further optimizations proved that the above-described one-pot protocol proceeded reliably and reproducibly in 90% yield on a multi-gram scale (entry 10).[16] The NMR data as well as specific rotation of synthetic helicascolide C (**3**) were in good agreement with those reported in the literature.[3] When MeI was introduced prior to *t*-BuOK, the desired natural product can also be obtained, albeit in a lower yield (entry 11). To further expedite the synthetic route, we telescoped the *anti*-aldol reaction and the above-described cyclization/methylation (Scheme 3). The resulting aldol reaction was quenched with a solution of methanol in THF. The solution was then titrated with *t*-BuOK to smoothly provide a solution of the enolate form of lactone **14**, which was then subjected to methylation to give **3** by sequential addition of DMF and MeI. This unoptimized protocol directly delivered helicascolide C (**3**) in one flask and in a synthetically acceptable yield from known building block **10**, provided an expedited protocol for purification, and further reduced the overall step count.

We then focused our attention on the late-stage reduction of the C3-keto group (Scheme 4). Unfortunately, initial screening of various reducing agents failed to directly convert **3** to **1** or **2** without reducing the ester functionality. In some cases, such as treatment with L-selectride at low temperature, an epimeric mixture of β-keto- δ-lactols **16** was isolated in 88% yield. Nevertheless, global reduction of **3** with 5 equiv of $NaBH_4$ smoothly furnished **17** in nearly quantitative yield albeit as an inseparable mixture. Careful analysis of the NMR spectra of the mixture confirmed the compounds are epimeric at the anomeric carbon (C1), and the configuration of C3 was determined to be (*R*) from the diagnostic NOE correlations of each anomer. These structures were confirmed by successful elaboration of **17** to helicascolide B (**2**) via MnO_2 oxidation.

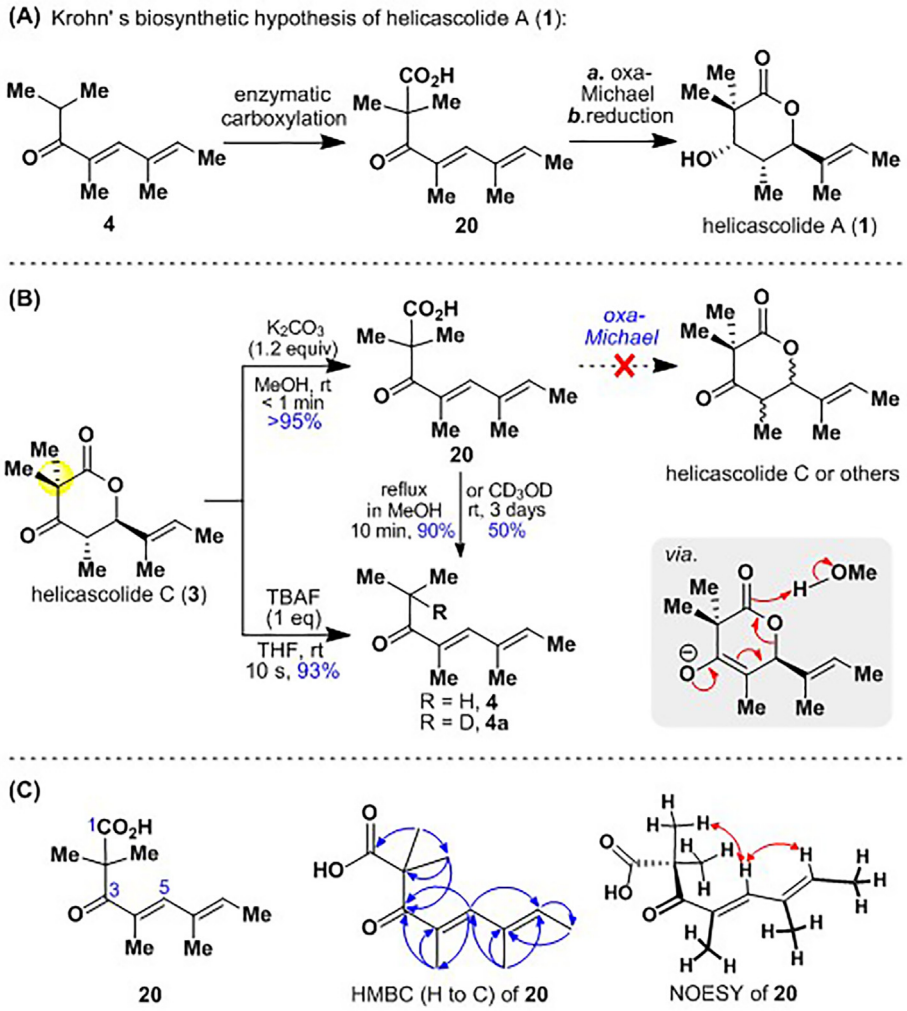
To override the intrinsic 1,3-diaxial strain of axial hydride delivery, a hindered reagent like $LiBHEt_3$ was presumed to deliver an axial alcohol through equatorial attack of the ketone.[17] At this point, the crude ^{1}H NMR spectrum of the organic layer taken immediately after work-up indicated that a new pair of anomeric (3*S*)-lactols **18** were formed as the major products in a moderate ratio of 2.7:1. Surprisingly, during the conventional work-up procedure, less polar component **19** was isolated, and after extensive



Scheme 3. Expedite "one-pot" aldolization/cyclization/alkylation of the known β-keto imide **10**.



Scheme 4. Divergent synthesis of helicascolide A (**1**) and B (**2**) via late-stage reduction.



Scheme 5. Biosynthetic relationships between helicascolide C (**3**) and **4**.

NMR analysis, **19** was determined to be a cyclic ethylboronate derivative of **18**.[18,19] Boronate **19** could be isolated in 51% yield from the chromatographically inseparable lactols **17** and **18**, thus providing an opportunity for the establishment of the correct stereochemistry at C3 for helicascolide A (**1**). As anticipated, heating **19** on neat silica gel yielded (3*S*)-lactol **18** in 86% yield as a mixture of anomeric isomers, which were further subjected to MnO_2 oxidation to give helicascolide A (**1**) in 85% yield. Gratifyingly, direct oxidation of cyclic ethylboronate **19** under the same reaction conditions also provided **1** in excellent yield (89%). The NMR spectra and optical rotation of the synthetic samples and natural helicascolides A (**1**) and B (**2**) were identical.[2]

It is also noteworthy that, during the optimization of the cyclization/alkylation cascade, methyl dienoate **15** was isolated as a side product, albeit in very low yield (<5%). We were aware of the structural similarity between this compound and an acid intermediate in Krohn's biogenesis proposal (Scheme 5 A).[4] Corresponding acid **20**, arising from enzymatic carboxylation of naturally occurring **4**, was suggested to be biosynthetically involved in the construction of the lactone ring of helicascolides through an oxa-Michael addition. We considered that the reverse process might be thermodynamically more favorable. To test our hypothesis, helicascolide C (**3**) was treated with biocompatible conditions like K_2CO_3 in methanol at ambient temperature. Interestingly, the ring-opening process was rapid and completed within minutes. The ring opening resulted in polar compound **20**, which, based on extensive NMR analysis, had a dienoic acid structure (Scheme 5 C).[20,21] This observation also mechanistically accounts for the formation of side product **15** via the *O*-methylation of an intermediate carboxylate. However, with β-keto acid **20** in hand, all attempts to realize the putative intramolecular oxa-Michael-type addition[4] only resulted in decarboxylation to form a less polar, UV-active material. The spectroscopic data were consistent with those reported for isopropyl ketone **4**.[4] The conditions tested for the oxa-Michael-type addition were as follows: (1) heating a salt-free solution of **20** in methanol for 10 min, which led to the isolation of **4**; (2) storage of a solution of **20** in *d*4-methanol at room temperature for 3 days, which resulted in 50% conversion to the C2-deuterated analogue **4a**, as indicated by NMR analysis (Fig. S1);[22] (3) treatment of a solution of **20** in THF with TBAF at room temperature, which resulted in the rapid generation of isopropyl ketone **4**, and intermediate β-keto acid derivatives were not detected by either TLC or NMR analyses.[23] The facile one-pot elimination and subsequent decarboxylation of **3** under mild conditions suggested a more plausible biogenesis of **4**.

In summary, we have developed a cyclization/alkylation approach for the efficient total synthesis of helicascolide C (**3**) in only two steps from chiral auxiliary-based β-keto imide **10**. The synthetic route can be further shortened by combining aldol reaction and cyclization/methylation, which provided a platform for other bioactive natural products bearing a critical δ-lactone ring system with *gem*-dimethyl substitution at C2. Based on the practicability of the new route, other congeners of the family could be divergently obtained with additional two steps. Moreover, a chemical intermediacy of β-keto acid derived from eliminative ring-opening of helicascolide C (**3**) implicates a revised biogenesis of the decarboxylative derivative **4**. Such biogenesis proposal may be also possible to form similar natural products through decarboxylation of β-keto esters with or without cooperation of individual enzymes.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.10.021.

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18. Data for *cyclic ethylboronate* ***19***: **TLC** (petroleum ether/ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.81; $[\alpha]_D^{25}$ = +2.7 (*c* = 0.69 in $CHCl_3$); **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.7 ppm; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.52 (qq, *J* = 6.8, 0.8 Hz, 1H, ***H***C_7), 4.77 (d, *J* = 1.6 Hz, 1H, ***H***C_1), 3.60 (br t, *J* = 2.0 Hz, 1H, ***H***C_3), 3.53 (d, *J* = 11.2 Hz, 1H, ***H***C_5), 2.09 (m, 1H, ***H***C_4), 1.66 (s, 3H, ***H*****$_3$**C_{11}), 1.62 (d, *J* = 6.4 Hz, 3H, ***H*****$_3$**C_{12}), 1.12 (s, 3H, ***H*****$_3$**C_8), 1.00 (s, 3H, ***H*****$_3$**C_9), 0.96 (t, *J* = 7.2 Hz, 3H, ***H*****$_3$**C_{14}), 0.80 (q, *J* = 7.2 Hz, 2H, ***H*****$_2$**C_{13}), 0.78 (d, *J* = 6.8 Hz, 3H, ***H*****$_3$**C_{10}) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 132.4 (**C_6**), 125.4 (**C_7**H), 97.4 (**C_1**H), 77.8 (**C_3**H), 77.5 (**C_5**H), 35.4 (**C_2**), 31.8 (**C_4**H), 23.1 (**C_9**H_3), 21.7 (**C_8**H_3), 14.4 (**C_{10}**H_3), 13.2 (**C_{12}**H_3), 11.2 (**C_{11}**H_3), 8.1 (**C_{14}**H_3) ppm; **IR** (thin film): ν_{max} = 2962, 2934, 2878, 1739, 1461, 1404, 1378, 1328, 1266, 1217, 1188, 1106, 1072, 1048, 1030, 959, 935, 816, 758, 747 cm^{-1}; **HRMS-DART** (*m/z*): calcd. for $C_{14}H_{26}O_3{}^{10}B[M+H]^+$: 252.2006, found: 252.2004.
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20. Data for β-keto acid **20**: **TLC** (petroleum ether/ethyl acetate = 4:1 v/v, $KMnO_4$): R_f = 0.01; **^{1}H NMR** (400 MHz, CD_3OD): δ = 7.03 (s, 1H, ***H***C_5), 5.70 (q, J = 7.2 Hz, 1H, ***H***C_7), 1.92 (s, 3H, ***H*****$_3$**C_{10}), 1.84 (s, 3H, ***H*****$_3$**C_{11}), 1.74 (d, J = 7.2 Hz, 3H, ***H*****$_3$**C_{12}), 1.33 (s, 6H, ***H*****$_3$**C_8, ***H*****$_3$**C_9) ppm; **^{13}C NMR** (100 MHz, CD_3OD): δ = 206.8 (**C_3**=**O**), 182.6 (**C_1**=**O**), 144.3 (**C_5**H), 134.6 (**C_6**), 132.9 (**C_4**), 131.4 (**C_7**H), 56.3 (**C_2**), 26.2 (**C_8**H_3, **C_9**H_3), 16.3 (**C_{11}**H_3), 14.6 (**C_{10}**H_3), 14.1 (**C_{12}**H_3) ppm; **IR** (thin film): ν_{max} = 3394, 2991, 2965, 2928, 2864, 1643, 1617, 1575, 1396, 1348, 1310, 1243, 1158, 1048, 1034, 896, 845 cm^{-1}. **HRMS-ESI** (m/z): calcd. for $C_{12}H_{18}O_3Na$ $[M+Na]^+$: 233.1148, found: 233.1147.
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23. For C2-enolizable lactone **14**, decarboxylation reactions using methanolic K_2CO_3 or TBAF under similar conditions only resulted in recovery of starting materials, and elimination products were not formed to any extent.