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SHORT COMMUNICATION

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Stereocontrol with Lithium Trimethylzincate toward Gibberellin Synthesis

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Substrate control in target-oriented synthesis is generally important in establishing the required stereogenic center rather than reagent control. During the course of the total synthesis toward Gibberellin A_3 (**1**), a model compound (**21**) as the A-ring of **1** was accomplished in five overall steps with an overall yield of 15 %, starting from furfural through conjugate addition of lithium trimethylzincate to oxabicyclo[2.2.1]heptadienedicarboxylic ester (**2**) as the key step. Relative to more common lithium dimethylcuprate or aluminum reagents, this zincate complex showed a complete selectivity with higher reactivity than with other simple enone compounds. The incoming methyl group was 100 % selective from the ring oxygen side of **2**, and the enolate intermediate can be protonated stereoselectivly without the bridge-oxygen-ring opening.

Organic synthesis utilizes a variety of organometallic reagents, which activate the substrate molecules and express unique chemoselectivity and stereoselectivity. Various kinds of organozinc reagents are known in organic synthetic methodology such as the Clemmensen reduction, the Reformatsky reaction, the Simmons–Smith reaction, the Staudinger ketene cycloaddition, the Negishi reaction, among others. Isobe et al. first reported in 1977 that lithium trialkylzincate, $R_3ZnLi{\cdot}2LiX$, reagents (R = Me, *n*Bu; *s*Bu, *t*Bu, Ph, etc.) undergo conjugate addition to α,β-unsaturated ketones such as cyclohexenone and cyclopentenones.[1] Lithium trimethylzincate(II) was directly prepared from zinc chloride or its non-hygroscopic tetramethylethylenediamine crystals (TMEDA-$ZnCl_2$) and 3 equiv. MeLi·LiBr in THF solvent.[1] Seebach et al. reported enantioselective 1,4-addition with the zincate complex with chiral amine ligands in 1979. Watson et al. confirmed the conjugate addition in 1986.[2] Yamamoto et al. also reported an asymmetric conjugate addition of the zincate complex,[3] which they later applied to several total syntheses of natural products.[4] There have been extensive studies recently on the structure and reactivity of the zinc reagents including multinuclear catalysis for copper-zinc reagents.[5]

We became interested in the further development of zincate reagents in an application towards the synthesis of the A-ring in the structure of several Gibberellins, a class of important plant hormones, as represented by GA_3 **1** (Figure 1). Six GA_n analogs (*n* = 3, 7, 30, 32, 68, and 80) feature the same substructure as **A** (Scheme 1).[6]

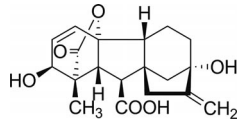
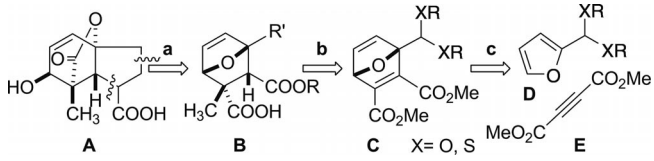


Figure 1. Structure of Gibberellin A_3 (**1**).



Scheme 1. Retrosynthesis of the A-ring of Gibberellin A_3 aiming at the use of lithium trimethylzincate.

To assure the correct complex stereochemistry of **A** (Scheme 1), the key features of such a synthesis must be the strict steric control of the transformation at the stereogenic carbon atoms in a cyclohexene precursor such as **C** (Scheme 1). To ensure the *trans*-stereochemical correlation at the two allylic positions, we planned a lactone ring formation with stepwise opening from the bridge oxygen (**B**). However, the selective introduction of a methyl group in step **b** from the bridge-oxygen side of precursor **C** poses a challenge. Different acetal moieties are available for **C** through a Diels–Alder reaction between a protected furfural **D** and dimethyl but-2-ynedioate **E**. In fact, this oxabicyclo[2.2.1]heptadiene (X = O or S) compound was readily prepared in good yields by heating. Now selective conjugate addition for the methyl group to **C** was examined.

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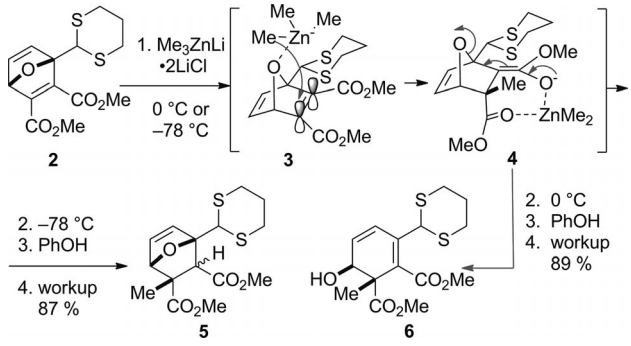
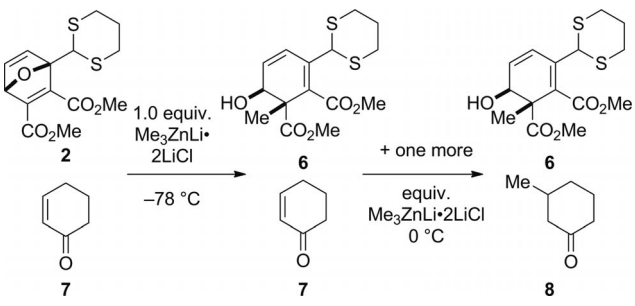
First lithium trimethylzincate reagent was tried with dithioacetal **2** (**C**, X = S) to see whether its use would address the stereochemical problem. Lithium trimethylzincate (Me_3ZnLi) was prepared by mixing 3.3 equiv. MeLi·LiBr and 1.1 equiv. $ZnCl_2$ solution in THF at 0 °C,[1] and this zincate was allowed to react with **2** at this temperature for 30 min. The following aqueous workup afforded a crystalline product **6**, and the structure was determined by X-ray analysis. The methyl group was stereo- and regioselectively introduced by an assumed chelative interaction as shown in **3** and **4**. The product **6** was obtained in 89% yield. Addition of the proton source at 0 °C afforded **6** (Scheme 2). We confirmed that the zinc enolate **4** did not open the ether ring at –78 °C but did so at higher temperatures below 0 °C. In order to avoid the ether ring opening to **6**, the lithium trimethylzincate complex (prepared at 0 °C) was cooled down to –78 °C, to which **2** was added, and the temperature was maintained for 30 min. Quenching of the reaction with 2 equiv. phenol in THF solution at –78 °C before aqueous workup afforded **5** as a mixture of diastereomers **5a** and **5b** (in a ratio of 1.6:1) in 87% yield. These results imply that the bridge-oxygen side is more chelative to deliver the methyl group in a complete stereoselective manner.



Scheme 2. Addition of lithium trimethylzincate to oxabicyclo-[2.2.1]heptadiene gives enolate **4** which can lead to **5** or **6** by quenching at different reaction temperatures.

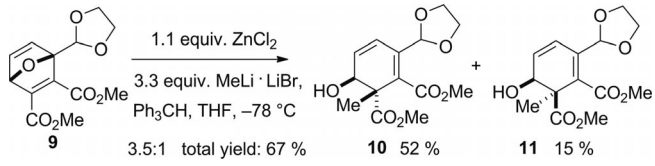
A difference in the nucleophilic reactivity of lithium trimethylzincate could be observed by directly comparing the two typical electrophiles such as the unsaturated diester **2** and the simple enone **7** (Scheme 3). Only 1.0 equiv. lithium trimethylzincate reagent in THF solvent (as described above) was placed in a flask, which was then cooled to –78 °C.



Scheme 3. Competitive addition of lithium trimethylzincate to **2** and **7**.

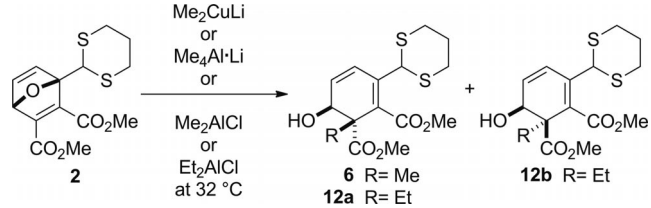
A solution containing equivalent amounts of **2** and **7** was added at the same time to this solution, and the reaction temperature was then gradually allowed to reach 0 °C. After workup, the crude reaction products were analyzed by NMR spectroscopy to show that the maleic diester substructure of **2** disappeared at a faster rate than **7** (details of the data can be seen in the Supporting Information). The simple enone **7** was demonstrated to react at 0 °C or higher to give **8**. Such a difference in reactivity may be attributed to chelation-driven preferred activation of the diester carbonyl groups by the zinc reagent.

Addition of Me_3ZnLi to **9** (**C**, X = O as ethylene acetal), on the other hand, afforded different stereoisomeric products such as **10** and **11** (Scheme 4). The selectivity changed in the case of ethylene acetal **9** as a result of some additional coordination, and the products were analyzed as a mixture of isomers such as **10** and **11** (for detail see ref.[11] and the Supporting Information). The 1,3-dithiane moiety seems therefore to be indispensable for the regioselectivity, in addition to the directing of the methyl addition from the β-face by the bridge oxygen atom.



Scheme 4. Addition of the lithium trimethylzincate complex to ethylene acetal precursor **9** gives **10** and **11** with Me from the bridge-oxygen side but without regioselectivity.

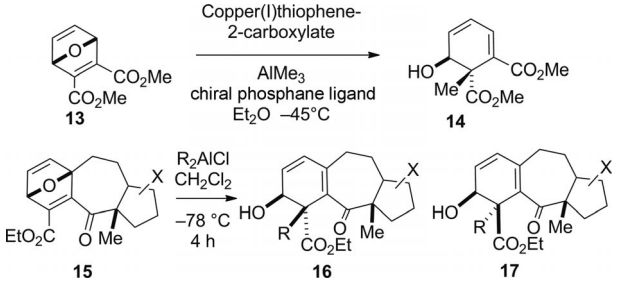
Addition of Me_2CuLi (lithium dimethylcuprate) to **2** at –78 °C instead of Me_3ZnLi largely yielded **5** together with the bridge-opening product **6**, even when the reaction was quenched with a proton source at –78 °C (Scheme 5). In this case, the intermediate copper enolate might change to lithium enolate in equilibrium at a much faster rate, which causes the ring opening at –78 °C.[7] In all of these cases, conjugate addition of the zincate complexes was accompanied by ether-ring opening.



Scheme 5. (a) Me_2CuLi: **5** (57% yield) plus **6** (14%) (quenched at –78 °C). (b) Me_4Al·Li (Me_3Al·MeLi +LiCl, LiBr, NaBr): **6** (55% yield). (c) Me_2AlCl (from *t*BuCl+Me_3Al): **6** (55% yield). (d) Et_2AlCl/CH_2Cl_2: **12a** and **12b** (ca. 1:1, in 81% yield).

Alexakis et al. reported the dinuclear catalysis with a Zn- or Al-ate complex and CuTC [CuTC = copper(I)thiophene-2-carboxylate] in a similar addition to dimethyl 7-oxabicy-

clo[2.2.1]heptadienedicarboxylate without a substituent at –40 °C to obtain the dienol in quantitative yields, with complete stereospecificity of the incoming nucleophile *cis* to the hydroxy group.[8] Yang et al. reported an aluminum reagent involved in a similar conjugate addition to **15**, which provides largely **16** with ring opening.[9] Thus, diene alcohol products of type **6** are formed stereoselectively. For aluminum reagents, a cationic mechanism[10] might be at work (Scheme 6).[11]



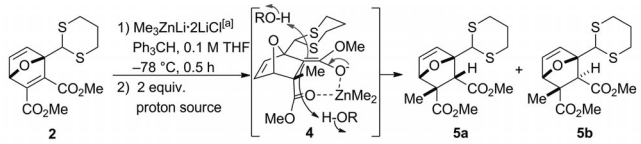
Scheme 6. Oxygen-atom-directed conjugate addition to the unsaturated diester.

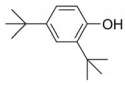
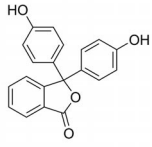
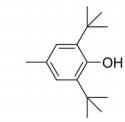
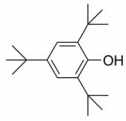
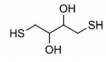
In our own experiments on **2**, treatment with tetramethylaluminumate reagent Me_4AlLi (prepared from $AlMe_3$ and MeLi) or Me_2AlCl (prepared from *t*BuCl and Me_3Al) did not afford any addition product below 0 °C only starting material. But at higher temperatures such as 32 °C, it afforded **6** in 55% yield in the presence of additional salts LiCl (LiBr or NaBr)[12] (Scheme 5). Treatment of **2** with dimethylchloroaluminum, which was prepared from *tert*-butyl chloride and trimethylaluminum, also provided **6** at room temperatures. Diethylchloroaluminum in dichloromethane, on the other hand, yielded a mixture of **12a** and **12b** in 81% total yield. The incoming ethyl group of the minor product **12b** was opposite to the bridge oxygen atom.[11]

Obviously the fate of the zinc enolate is important in obtaining the protonated products of type **5** without ring opening. Thus, we embarked on a systematic investigation of the protonation conditions. Use of various proton sources toward the intermediate **4** yielded either **5a** or **5b** as shown in Table 1. Each proton-source reagent was added in THF solution directly to the reaction mixture at –78 °C after 30 min of mixing **2** with Me_3ZnLi. The products were isolated, crystallized, and analyzed by X-ray crystallography to be **5a** (m.p. 81.8 °C, δ(Me) = 1.65 ppm) and **5b** (m.p. 114.8 °C, δ(Me) = 1.40 ppm), respectively. The results are summarized in Table 1. Among the four phenols (Entries 1–4), the bulkier ones provide less amounts of **5b**, and the smaller cerium chloride (Entry 5) afforded **5a** as the major product in 88% yield. In contrast, phenolphthalein gives only **5b** as the dominant product (Entry 6), while dithiothreitol did not give a preferential product (Entry 7). The zinc enolate remains stable at –78 °C without ring opening, and it can be protonated in a stereoselective manner.

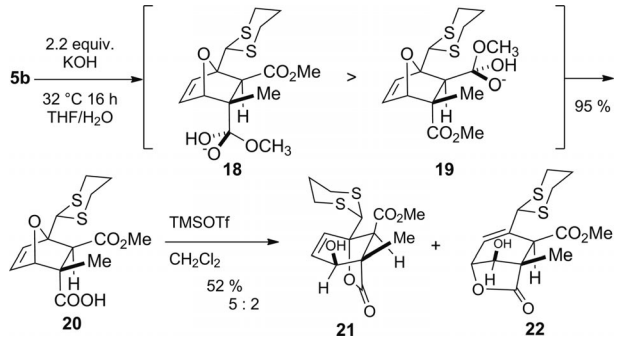
For subsequent formation of the γ-lactone (step **a** in Scheme 1), the protonated product dimethyl ester **5** was hydrolyzed under alkaline conditions. Attempted selective hydrolysis of the diesters **5a** or **5b** (KOH in THF/H_2O) was only successful for the latter, which gave the monoacid **20** in 95% yield (Scheme 7). This selectivity might be attributed to the difference in the steric interaction of the possible tetrahedral intermediates **18** and **19**; thus, **19** must have a greater steric interaction with the surrounding substructures than **18**. This assumption is supported by the fact that no selectivity was found with **5a**, which afforded a 1:1 mixture of the corresponding monoacids under the same conditions. In both cases, the second hydrolysis of the remaining ester group became very slow under these conditions because of the anion-repulsive interaction required for OH^- to attack the carboxylate anion molecule to isolate the monoacids in high yields.

Table 1. Proton-source effects to selective formation of **5a** or **5b**.



Entry	Proton source	Yield[b]	Ratio (**5a**:**5b**)[c]	Entry	Proton source	Yield[b]	Ratio (**5a**:**5b**)[c]
1		87 %	62:38	*5*	$CeCl_3·7H_2O$	88 %	80:20
2		81 %	66:34	*6*		90 %	29:71
3		88 %	68:32				
4		88 %	70:30	7		67 %	43:57

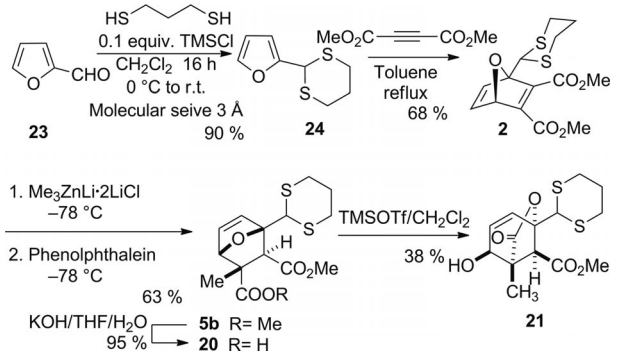
[a] Prepared by $ZnCl_2$ and MeLi·LiBr, with stirring for 30 min at 0 °C. [b] Combined yield of **5a** and **5b**. [c] Separated ratio.



Scheme 7. Selective hydrolysis of the diester **5b** to **20** and γ-lactone formation.

The anticipated lactonization was examined with various kinds of Lewis acids. Among those, trimethylsilyl triflate afforded the γ-lactone **21** (ν 1783 cm^{-1}) and its isomeric lactone **22** (ν 1790 cm^{-1}) in a 5:2 ratio in 52% combined yield (Scheme 7).

In summary, the synthesis of a model for the A-ring of Gibberellin **21** was accomplished in five overall steps with a 15% overall yield, starting from commercially available furfural **23** and the use of a lithium trimethylzincate reagent as the critical step (Scheme 8). Relative to more common cuprate or aluminate reagents, the zincate complex showed a differentiated high specific activity. Further research on the conjugate addition chemistry of the zincates is ongoing.



Scheme 8. Synthesis of Gibberellin A-ring via lithium trimethylzincate addition.

Experimental Section

Dimethyl 3-(1,3-Dithian-2-yl)-6-hydroxy-1-methylcyclohexa-2,4-diene-1,2-dicarboxylate (6): Under Ar (or nitrogen) atmosphere, MeLi·LiBr (2.2 M in Et_2O solution, 1.54 mL, 3.38 mmol, 3.3 equiv.) was added to a mixture of dry THF (5.3 mL), $ZnCl_2$ (154 mg, 1.13 mmol, 1.1 equiv.), and Ph_3CH (as an indicator, 1.0 mg) at 0 °C. The mixture was stirred for 30 min at the same temperature and then cooled to –78 °C. 7-Oxanorbornadiene **2** (337 mg, 1.03 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise at –78 °C; the cooling bath was then removed, and the mixture was stirred for 30 min at 0 °C. The reaction was quenched by addition of phenol (C_6H_5OH, 0.18 mL, 2.05 mmol, 2.0 equiv.) at 0 °C with stirring for 30 min, and the mixture was then poured into saturated NH_4Cl (pH = 4, 10 mL) solution at 0 °C. The mixture solution was extracted with diethyl ether (3 × 10 mL) and brine (30 mL), dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc/hexane, 2:8) to afford alcohol **6** (313 mg, 0.91 mmol, 89%) as a yellow solid. R_f = 0.71 (EtOAc/hexane, 2:3). M.p. 136.8–137.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.75–1.85 (m, 1 H), 1.92 (d, J = 5.6 Hz, 1 H), 2.06–2.11 (m, 1 H), 2.79–2.85 (m, 2 H), 2.94–3.04 (m, 2 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 4.87–4.89 (m, 1 H), 5.94 (dd, J = 2.0, 9.6 Hz, 1 H), 5.97 (s, 1 H), 6.38 (dd, J = 2.8, 9.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 24.5, 30.3, 30.7, 47.1, 51.5, 52.4, 54.0, 72.8, 123.6, 129.0, 136.1, 139.9, 166.7, 175.9 ppm. HRMS (EI): calcd. for $C_{15}H_{20}O_5S_2$ 344.0752; found 344.0753.

Methyl Addition to 2 with Organozinc Reagents: Under Ar (or nitrogen) atmosphere, MeLi·LiBr (2.2 M in Et_2O solution, 1.61 mL, 3.54 mmol, 3.3 equiv.) was added to a mixture of dry THF (5.7 mL), $ZnCl_2$ (160 mg, 1.18 mmol, 1.1 equiv.), and Ph_3CH (as an indicator, 1.0 mg) at 0 °C. The mixture was stirred for 30 min at the same temperature and then cooled to –78 °C. 7-Oxanorbornadiene **2** (352 mg, 1.07 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise at –78 °C, and the mixture stirred for 30 min. The reaction was quenched by addition of phenol (C_6H_5OH, 0.19 mL, 2.14 mmol, 2.0 equiv.) at –78 °C with stirring for 30 min, and the mixture was then poured into saturated NH_4Cl (pH = 4, 10 mL) solution at 0 °C. The mixture solution was extracted with diethyl ether (3 × 10 mL) and brine (30 mL), dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc/hexane, 2:8) to afford both **5a** (199 mg, 0.578 mmol, 54%) and **5b** (121 mg, 0.353 mmol, 33%) as yellow solids.

Dimethyl (2*R,3*S**)-1-(1,3-Dithian-2-yl)-3-methyl-7-oxabicyclo-[2,2,1]hept-5-ene-2,3-dicarboxylate (5a):** R_f = 0.74 (EtOAc/hexane, 2:3). M.p. 79.3–81.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 3 H), 1.89–1.99 (m, 1 H), 2.02–2.11 (m, 1 H), 2.74–2.82 (m, 2 H), 2.98–3.03 (m, 2 H), 3.21 (s, 1 H), 3.59 (s, 3 H), 3.65 (s, 3 H), 4.47 (s, 1 H), 4.67 (d, J = 1.6 Hz, 1 H), 6.45 (dd, J = 1.6, 6.0 Hz, 1 H), 6.60 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 25.6, 29.0, 29.2, 45.6, 51.6, 51.7, 56.9, 58.6, 85.2, 94.6, 134.7, 136.5, 171.0, 172.6 ppm. HRMS (EI): calcd. for $C_{15}H_{20}O_5S_2$ 344.0752; found 344.0743.

Dimethyl (2*S,3*S**)-1-(1,3-Dithian-2-yl)-3-methyl-7-oxabicyclo-[2,2,1]hept-5-ene-2,3-dicarboxylate (5b):** R_f = 0.68 (EtOAc/hexane, 2:3). M.p. 114.3–114.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.80–1.91 (m, 1 H), 2.08–2.15 (m, 1 H), 2.79–2.85 (m, 2 H), 2.89–2.98 (m, 2 H), 3.24 (s, 1 H), 3.66 (s, 3 H), 3.72 (s, 3 H), 4.71 (d, J = 1.6 Hz, 1 H), 5.13 (s, 1 H), 6.39 (d, J = 6.0 Hz, 1 H), 6.54 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 25.5, 29.7, 30.4, 47.3, 51.2, 51.6, 52.2, 55.0, 84.6, 92.0, 136.5, 136.7, 170.8, 173.8 ppm. HRMS (EI): calcd. for $C_{15}H_{20}O_5S_2$ 344.0752; found 344.0758.

Effects of Different Proton Sources After Methylation of 2. General Procedure: Under Ar (or nitrogen) atmosphere, MeLi·LiBr (2.2 M in Et_2O solution, 0.46 mL, 1.01 mmol, 3.3 equiv.) was added to a mixture of dry THF (1.6 mL), $ZnCl_2$ (45.7 mg, 0.336 mmol, 1.1 equiv.), and Ph_3CH (as an indicator, 1.0 mg) at 0 °C. The mixture was stirred for 30 min at the same temperature and then cooled to –78 °C. 7-Oxanorbornadiene **2** (100 mg, 0.305 mmol, 1.0 equiv.) in THF (1.5 mL) was added dropwise at –78 °C, and the mixture was stirred for 30 min. The reaction was quenched by addition of different proton sources (in 2 mL THF, excluding phenol, and $CeCl_3·7H_2O$ was just added to the mixture solution, 0.610 mmol, 2.0 equiv.) at –78 °C with stirring for 30 min, and the mixture was then poured into saturated NH_4Cl (pH = 4, 5 mL) solution at 0 °C. The mixture solution was extracted with diethyl ether (3 × 5 mL) and brine (15 mL), dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc/hexane, 2:8) to afford compounds **5a** and **5b**. The details of results are shown in Figure 2.

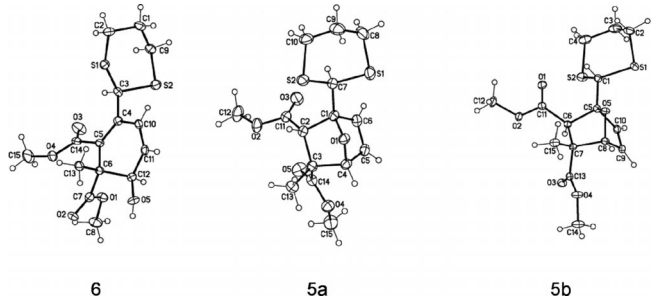


Figure 2. Ortep drawings of the crystal structures of **6**, **5a**, and **5b**.

Lactone 21: Yellow solid. R_f = 0.38 (EtOAc/hexane, 2:3). M.p. 128.8–130.3 °C. IR: $\tilde{\nu}$ = 3399 (br.), 1783, 1712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.53 (3H, s), 1.94–2.03 (m, 1 H), 2.10–2.15

(m, 1 H), 2.50–2.56 (m, 2 H), 3.13–3.28 (m, 2 H), 3.71 (s, 3 H), 3.94 (d, J = 11.6 Hz, 1 H), 3.96 (s, 1 H), 4.04 (s, 1 H), 4.05–4.09 (m, 1 H), 6.09 (dd, J = 3.2, 9.6 Hz, 1 H), 6.48 (d, J = 9.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 24.5, 26.4, 26.5, 42.9, 48.7, 52.9, 54.3, 67.6, 88.3, 129.5, 135.0, 170.2, 176.3 ppm. HRMS (EI): calcd. for $C_{14}H_{18}O_5S_2$ 330.0596; found 330.0594.

Lactone 22: Yellow solid. R_f = 0.36 (EtOAc/hexane, 2:3). M.p. 128.7–129.6 °C. IR: $\tilde{\nu}$ = 3384 (br.), 1790, 1714 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.84–1.93 (m, 1 H), 2.03–2.09 (m, 1 H), 2.76–2.82 (m, 3 H), 2.85–2.91 (m, 1 H), 3.63 (s, 3 H), 3.84 (s, 1 H), 4.15 (dd, J = 4.8, 9.6 Hz, 1 H), 4.26 (s, 1 H), 4.79 (dd, J = 4.8, 5.6 Hz, 1 H), 5.07 (d, J = 9.6 Hz, 1 H), 6.67 (d, J = 6.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 24.9, 30.2, 30.2, 45.1, 47.5, 49.9, 53.7, 72.7, 73.2, 128.1, 139.6, 173.3, 176.4 ppm. HRMS (EI): calcd. for $C_{14}H_{18}O_5S_2$ 330.0596; found 330.0600.

Supporting Information (see footnote on the first page of this article): Gibberellin congeners, complete experimental details, competitive experimental details, crystal structures.

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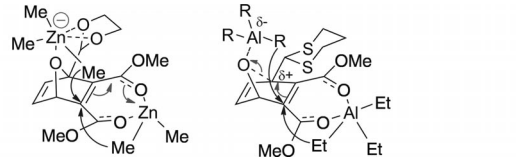

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