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A Concise Route to Branched Erythrono-γ-lactones. Synthesis of the Leaf-Closing Substance Potassium (±)-(2*R*,3*R*)-2,3,4-Trihydroxy-2-methylbutanoate

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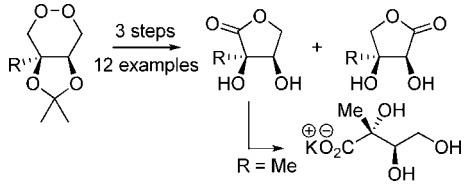
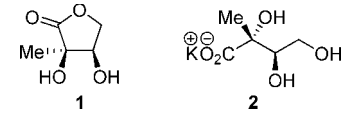


A series of 1,2-dioxanes **3** were ring-opened with Co(SALEN)$_2$ to furnish lactol regioisomers **4** and **5** (86−99% yield). The lactols were oxidized to γ-lactones **8** and **9** (72−96% yield) and deprotected to afford the 2-*C*- and 3-*C*-alkyl and aryl branched erythrono-γ-lactones **1**, **6**, and **7** (65−94% yield), including the natural plant lactone (±)-2-*C*-D-methylerythrono-1,4-lactone **1**. The latter compound was treated with aqueous potassium hydroxide to afford potassium (±)-(2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate **2**, which is a leaf-closing substance of *Leucaena leucocephalam*.

Many plants close their leaves during the evening and open them in the morning according to an innate biological rhythm known as nyctinasty, which is important for their survival.[1,2] This process appears to be governed by the relative concentration of discrete bioactive compounds produced within the plant, designated as either leaf-opening substances or leaf-closing substances, depending on their function.[3,4] It has been speculated that each family of nyctinastic plants possesses a unique set of opening/closing substances, which is supported by the isolation of many individual regulating compounds from a wide variety of plants.[3,5−10] Recently Ueda et al. identified potassium (2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate **2** (Figure 1) as a leaf-closing substance of the tropical legume *Leucaena leucocephalam*.[11]



1 **2**

FIGURE 1. Plant lactone **1** and the potassium carboxylate salt **2**.

Presumably, the carboxylate salt is formed in vivo from 2-*C*-methyl-D-erythrono-1,4-lactone **1**, which itself has been isolated from the leaves of several legumes including *Astragalus lusitanicus*,[12] *Cicer arietinum* (chickpea),[13] and *Hymenoxys richardsonii*,[14] and identified as a metabolite in the mevalonate-independent pathway for terpenoid biosynthesis.[15] Given the interesting biological functions of the plant compounds **1** and **2**, it is surprising there have been few reported syntheses of both the racemic and enantiopure compounds.[16−20]

We have previously demonstrated that 4-substituted 1,2-dioxines can be converted to erythro-sugar derivatives via a dihydroxylation, reduction strategy (Scheme 1, route a).[21] Utilizing the acetonide-protected 4,5-dihydroxy-1,2-dioxanes **3** it was envisaged that our methodology could be extended to provide a new route to plant lactone **1** and the leaf-closing substance **2**, as well as providing a general route to other known and novel branched erythrono-γ-lactones. To the best of our knowledge no general method to access compounds of this type has been reported. The proposed approach (route b) relies on homolytic cleavage of acetonide protected 1,2-dioxanes **3** to give lactols **4** and **5**, followed by oxidation to the corresponding lactones, and deprotection to yield the target erythrono-γ-lactones.

We now wish to report a concise and efficient route to alkyl and aryl branched erythrono-γ-lactones and the synthesis of the leaf-closing substance **2** in 7 steps from isoprene.

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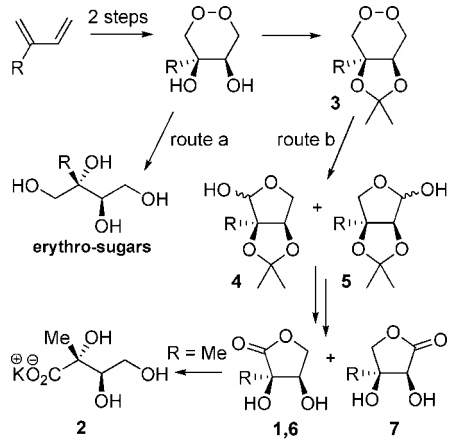
SCHEME 1. Proposed Route to Branched Erythrono-γ-lactones 1, 6, and 7, and the Leaf-Closing Substance 2



SCHEME 2. $Co(SALEN)_2$ Ring-Opening of Peroxy Acetonides 3

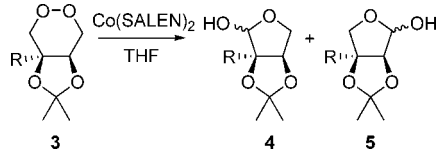


TABLE 1. $Co(SALEN)_2$ Ring-Opening of Peroxy Acetonides 3

entry	R	products	yield (%)[a]	**4**:**5**[b]
1	Ph	**4a**, **5a**	99	60:40
2	*c*-C_6H_{11}	**4b**, **5b**	97	43:57
3	1-Ad	**4c**, **5c**	98	45:55
4	Me	**4d**, **5d**	86	53:47
5	*n*-C_6H_{13}	**4e**, **5e**	99	47:53
6	Bn	**4f**, **5f**	98	46:54

[a] Refers to the combined isolated yield of both regioisomers. [b] The ratio was determined by isolated mass after chromatography.

Our study commenced from the acetonide protected peroxy diols **3** (Scheme 1). The synthesis of these compounds is amenable to a wide range of substituents. Moreover, optically enriched peroxy acetonides **3** can be synthesized by using the Sharpless asymmetric dihydroxylation.[21,22] The use of Co(II) for ring-opening endoperoxides is well-known.[23−26] When the peroxy acetonides **3** in the present study were treated with $Co(SALEN)_2$ a ∼1:1 mixture of lactol regioisomers **4** and **5** (Scheme 2) were obtained in excellent yields (Table 1). The regioisomers were easily separated by conventional column chromatography and hence this method proved to be an ideal entry for the synthesis of both series of erythrono-γ-lactones.

All of the aldoses were found to exist as mixtures of anomers solely in their cyclic furanose forms both when neat, as indicated by the absence of a carbonyl stretch in the IR spectra, and when in solution, as indicated by NMR. The regioisomers and their relative stereochemistry were determined by 1D/2D NMR, and unambiguously confirmed by single-crystal X-ray analysis of lactols **4c** and **5c**. The known erythrofuranoses **4d**[17] and **5d**[27] were spectroscopically consistent with the data reported in the literature.

TABLE 2. Ring-Opening of Peroxy Acetonides 1 with Various Reagents

entry[a]	R	reagent	conditions[b]	**4**:**5**[c]	yield (%)[d]
1	Ph	brucine	a	38:62	54[e]
2	Ph	quinine	a	40:60	46[e]
3	Ph	$FeSO_4 \cdot 7H_2O$	b	70:30	high[f]
4	*c*-C_6H_{11}	$FeSO_4 \cdot 7H_2O$	b	73:27	high[f]
5	1-Ad	$FeSO_4 \cdot 7H_2O$	b	80:20	high[f]
6	Me	$FeSO_4 \cdot 7H_2O$	b	68:32	high[f]
7	*n*-C_6H_{13}	$FeSO_4 \cdot 7H_2O$	b	74:26	high[f]
8	Bn	$FeSO_4 \cdot 7H_2O$	b	72:28	high[f]

[a] Reactions performed with 30−50 mg of 1,2-dioxane and stirred at room temperature until completion was observed by TLC. [b] Conditions: (a) 0.1 equiv of reagent in THF; (b) 1.6 equiv of reagent in THF/H_2O. [c] Ratio determined by ^1H NMR ($CDCl_3$) after 1 h at room temperature. [d] Combined yield. [e] Isolated yield. [f] Products were not purified. ^1H NMR showed complete conversion and minimal byproduct.

The method would, however, be of greater synthetic utility if the reaction was regioselective giving products enriched with regioisomer **4** or **5** depending on the reaction conditions. In a study by Nakano and Aguero, it was observed that $FeSO_4$-induced ring-opening of a specific epoxy-1,2-dioxane gave only one of two possible lactol products.[28] Consequently, 1,2-dioxane **4a** was exposed to the same conditions, resulting in a 70:30 mixture (entry 3, Table 2). While the reaction did not give the selectivity observed by Nakano and Aguero, it was a distinct improvement over $Co(SALEN)_2$, prompting a detailed investigation into how other reagents influence the ratio of lactols obtained from ring-opening. From the reagents evaluated (see SI for a complete list) the highest selectivity for lactol products **4** was observed for $FeSO_4$, and the remainder of the 1,2-dioxanes were treated under the same conditions. In each example a significant preference for lactol **4** was observed (entries 4−8), most notably for the bulky adamantyl-substituted compound (entry 5).

Interestingly, the use of the chiral amine bases brucine and quinine favored formation of lactol regioisomer **5a** (entries 1 and 2); however, the reactions were slow returning a yield of only ∼50% after 2 weeks.

The results constitute a significant improvement over the $Co(SALEN)_2$ conditions and suggest that careful reagent optimization could improve the regioselective outcome of the ring-opening in a predictable manner.

With lactols **4** and **5** in hand, the anomeric alcohol had to be oxidized to produce the desired erythrono-γ-lactones **8** (Scheme 3) and **9** (Scheme 4). There are a variety of oxidation methods available for this transformation, which relies on the lactols to remain in their cyclic furanose forms.

A method for lactol oxidation used extensively by Fleet and co-workers involves treatment with elemental bromine in a solution buffered with carbonate.[29−31] Unfortunately, this method gave only trace amounts of the desired lactones,

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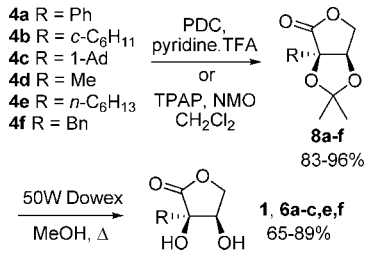
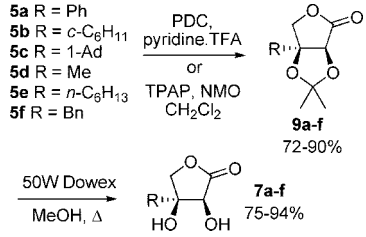
SCHEME 3. Synthesis of 2-Branched Erythrono-γ-lactones



SCHEME 4. Synthesis of 3-Branched Erythrono-γ-lactones



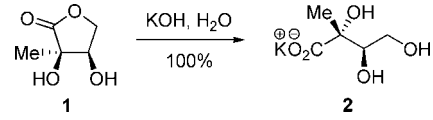
accompanied by a complex mixture of byproduct. As an alternative the oxidant PDC was tried and showed clean conversion to the desired lactones, but very long reaction times were required even when PDC was used in excess. Addition of pyridinium trifluoroacetate improved the reaction rates significantly[32] (4−11 days) and all oxidations bar two were performed in this manner to give high yields of the acetonide-protected lactones **8** (Scheme 3) and **9** (Scheme 4). The oxidant TPAP[33] was tested on lactols **4e** and **5e** to see if the reaction could be accelerated further. Indeed the use of catalytic quantities of TPAP with NMO as a co-oxidant resulted in a substantial improvement over PDC, requiring less than 16 h for completion in excellent yield.

The structure of acetonide-protected lactones **8a**−**f** and **9a**−**f** was confirmed by NMR, IR, and mass spectroscopy, and the molecular structure of adamantyl-substituted lactone **8c** was further confirmed by single-crystal X-ray analysis. Known lactones **8d** and **9d** were spectroscopically identical with that previously reported.[16]

Acidic 50W Dowex resin was employed for the acetonide hydrolysis of γ-lactones **8a**−**f** (Scheme 3) and **9a**−**f** (Scheme 4). The acetonide group proved very resistant to hydrolysis, and required extended reaction times (1−11 days). This is presumably a result of steric hindrance at the tertiary alcohol, as evidenced by the fastest reaction times for the methyl-substituted lactones **8d** and **9d**, whereas the slowest times observed were for adamantyl-substituted lactones **8c** and **9c** (see the SI). In some instances a small amount of lactone hydrolysis to give the free carboxylic acid was also observed. Despite extended reaction times all lactone diols **1**, **6**, and **7** were isolated in good to excellent yields and high purity.

The novel 2- and 3-substituted erythrono-γ-lactones **6a**−**c**,**e**,**f** and **7a**−**c**,**e**,**f** were fully characterized giving data consistent with the molecular structures. The structure of lactone **1** was confirmed as being the plant lactone (±)-2-*C*-D-methylerythrono-1,4-lactone by comparison of the NMR data with that

SCHEME 5. Synthesis of the Leaf-Closing Substance Potassium (±)-(2*R*,3*R*)-2,3,4-Trihydroxy-2-methylbutanoate 2



reported in the literature.[16,34] The structure of lactone **6c** was confirmed by single-crystal X-ray analysis.

Finally, (±)-2-*C*-D-methylerythrono-1,4-lactone **1** was treated with aqueous potassium hydroxide to quantitatively afford potassium (±)-(2*R*,3*R*)-2,3,4-trihydroxy-2-methylbutanoate **2**, a leaf-closing substance of *Leucaena leucocephalam* (Scheme 5).[11]

In summary, we have developed a general and efficient route to 2- and 3-aryl and alkyl branched erythrono-γ-lactones starting from known and easily accessible 1,2-dioxines. We have previously shown that asymmetric dihydroxylation of 1,2-dioxines gives enantioenriched 4,5-dihydroxy-1,2-dioxines.[21] Hence the work presented here can be extended to include the synthesis of optically active erythrono-γ-lactones.

Experimental Section

General Procedure for Ring-Opening Acetonide-Protected 1,2-Dioxanes 3 with Co(SALEN)$_2$. To a stirred solution of *N*,*N*′-bis(salicylidene)ethylene diaminocobalt(II) (0.05 mmol) in THF (5 mL) at ambient temperature was added 1,2-dioxane (1 mmol), and the reaction was left to stir until completion was observed by TLC (∼16 h). All volatiles were removed in vacuo, and the product was purified by column chromatography.

(±)-2,3-*O*-Isopropylidene-2-*C*-methylerythrofuranose 4d.[17] Major anomer: colorless oil (200 mg, 46%, 86% total). All analytical data were consistent with that previously reported (see the SI).

General Procedure for $FeSO_4$ Ring-Opening. To a stirred solution of acetonide-protected 1,2-dioxane (0.25 mmol) in THF (1.5 mL) was added a solution of $FeSO_4 \cdot 7H_2O$ (0.4 mmol) in H_2O (1 mL), and the mixture was stirred at ambient temperature until completion was observed by TLC (ca. 30 min). The reaction was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the organic layer was separated. The aqueous layer was extracted again with CH_2Cl_2 (10 mL). The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed in vacuo to give a crude mixture of ring-opened products. The residue was taken up in $CDCl_3$, and the ratio of isomers was determined by ^{1}H NMR integration.

General Procedure for PDC Oxidation of Lactols 4 (or 5) to Lactones 8 (or 9). To a solution of lactol (1 mmol) dissolved in anhydrous CH_2Cl_2 (10 mL) was added freshly prepared PDC[32] (2 mmol) and pyridinium trifluoroacetate salt (0.4 mmol). The resulting brown slurry was stirred vigorously under nitrogen until completion was observed by TLC (ca. 2−5 days). It is important to note that all TLC's were visualized with Hanessian stain, which was the only dip found that would visibly stain the lactones. Upon completion the solvent was removed, and the residue was carefully transferred onto a pad of silica with a 1:1 mixture of ether/hexane and eluted with the same solvent system to remove all of the chromium waste. The crude lactone was further purified by column chromatography to give analytically pure acetonide-protected erythro-γ-lactones.

(±)-2,3-*O*-Isopropylidene-2-*C*-methylerythrono-1,4-lactone 8d.[16] Colorless oil (115 mg, 86%). All analytical data were consistent with that previously reported (see the SI).

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(34) Interestingly, the NMR sample (in CD_3OD) showed formation of the open-chain acid,[36] which stabilized to give a constant 74:26 mixture of lactone and carboxylic acid. ^{1}H NMR spectra are supplied in the Supporting Information.

TPAP Oxidation of Lactols to Lactones. (±)-2,3-*O*-Isopropylidene-2-*C*-hexylerythrono-1,4-lactone 8e. Lactol **4e** (256 mg, 1.05 mmol) was dissolved in anhydrous dichloromethane (2.5 mL). Molecular sieves (0.25 g, 4 Å) and *N*-methylmorpholine *N*-oxide (0.25 g, 2.09 mmol) were added followed by tetrapropylammonium perruthenate (21 mg, 60 μmol). After being stirred at ambient temperature under nitrogen overnight the reaction mixture was filtered through a pad of Celite and the solid residue was washed with dichloromethane. The combined organic phases were concentrated in vacuo to give a black gum. Purification by DCVC[35] [i.d. 4 cm; 20 mL fractions; 4 × hexanes; 5−75% EtOAc in hexanes (v/v)−5% increments] gave lactone **8e** (0.24 g, 96%) as white needles. Mp 52−53 °C; R_f 0.35 (1:5 ethyl acetate/hexane); IR (nujol) 1777, 1249, 1223, 1170, 1075, 1006 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.25−1.37 (m, 6H), 1.39 (d, J = 0.5 Hz, 3H), 1.43 (d, J = 0.5 Hz, 3H), 1.43−1.49 (m, 2H), 1.79−1.88 (m, 2H), 4.27 (dd, J = 3.5, 11 Hz, 1H), 4.39 (d, J = 11 Hz, 1H), 4.52 (d, J = 3.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 22.4, 23.2, 26.6, 27.0, 29.3, 31.4, 32.1, 69.6, 78.8, 84.4, 112.8, 176.6; MS *m*/*z* (+EI) 242 (M^+, 3), 227 (100), 197 (3), 184 (21), 169 (33), 140 (7), 128 (13), 111 (23), 97 (15), 70 (79), 55 (46); HRMS calcd for (M + Na) $C_{13}H_{22}NaO_4$ 265.1416, found 265.1414; Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.68; H, 9.39.

General Procedure for Deprotection of Acetonides 8 (or 9) To Give Lactone Diols 1, 6, or 7. To a solution of acetonide-protected lactone (1 mmol) dissolved in MeOH (10 mL) was added activated 50W Dowex X8 resin (1 g), and the mixture was stirred at 70 °C until completion was observed by TLC (ca. 2−5 days). The reaction was allowed to cool and then filtered to remove the Dowex. Methanol was removed under reduced pressure and the residue was purified by column chromatography to furnish the pure lactone diols.

(±)-2-*C*-D-Methylerythrono-1,4-lactone 1.[16] Colorless solid (60 mg, 76%). All analytical data were consistent with that previously reported (see the SI).

(±)-Potassium 2,3,4-Trihydroxy-2-methylbutanoate 2.[11,16] Methylerythrono-1,4-lactone **1** (10 mg, 0.075 mmol) was dissolved in H_2O (1 mL) and the mixture was stirred with KOH (4.2 mg, 0.075 mmol) for 20 min. The water was removed in vacuo and the residue dried under high vacuum, and then taken up in D_2O for characterization. All analytical data were consistent with that previously reported (see the SI).

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Supporting Information Available: Experimental procedures, full characterization, ^{13}C NMR spectra, and ^{1}H NMR spectra for all compounds and crystallographic data and CIF files for **4c**, **5c**, **8c**, and **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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