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Mild and Chemoselective Lactone Ring-Opening with (TMS)ONa. Mechanistic Studies and Application to Sweroside Derivatives

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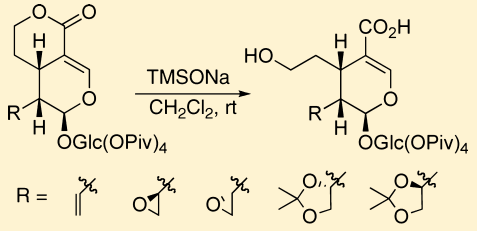
Supporting Information

ABSTRACT: Mild and chemoselective opening of lactones with sodium trimethylsilanolate in high yields and aprotic solvents is described. Kinetic studies demonstrate that the $B_{Ac}2$ mechanistic pathway is followed. Nucleophilic attack of silanolate onto the carbonyl of the lactone moiety is the rate-determining step. NaOH present as an impurity accelerates the reaction. The method was further applied to the base-sensitive and stable lactones derived from highly functionalized iridoid derivatives.



INTRODUCTION

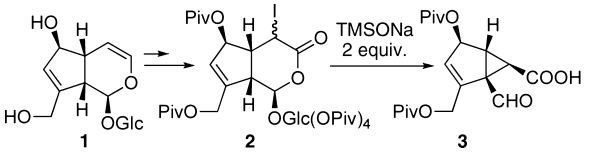
Hydroxy acids have found numerous applications in the agrochemical, pharmaceutical, and cosmetic industries.[1,2] Chiral hydroxy acids, common in nature, are renewable sources of biologically active products and synthetically useful synthons.[3] Stable and unreactive lactones with diverse architecture and varying degrees of complexity are frequent secondary metabolites.[4] Lactone ring-opening (LRO) under mild and selective conditions would, thus, be a straightforward strategy to access a large variety of polyfunctional hydroxy carboxylic acids.[5]

A variety of functional groups are incompatible with LRO procedures, which limits their use in organic syntheses. Current LRO methods confront several severe problems, including selectivity of ester cleavage, elimination reactions under basic conditions, and solubility in aprotic solvents. The LRO methods generally imply hydrolysis of the lactone[6] induced by strong bases[7−9] or acids,[10−12] usually in protic media. Various types of hydroxy carboxylic acid derivatives can be obtained by LRO employing N-, S-, or Se-nucleophiles.[3] Alternatively, reduction with hydrides or alkylation with organometallic compounds in the absence or presence of (TMS)X (X = halides, sulfonates)[3,13] may furnish interesting derivatives. The facility of the LRO can be correlated to the size of the lactone. Five-membered ring systems are favored over the open chain compounds, while six-membered lactones equilibrate with the hydroxy acid counterpart. For obvious reasons of ring strain release, LRO of small (three- and four-membered ring lactones) and medium (seven-, eight-, nine-, and ten-membered ring lactones) is easier than that of five- and six-membered rings.[14,15] Moreover, lactones that are annulated with other rings may resist LRO because of a too small entropy gain of the ring-opening. This may also be the case for polysubstituted lactones that are isomerized into hydroxy carboxylic acids. They lack full entropy of rotation due to partially blocked C−C rotation because of gauche steric interactions between the substituents.[3,14−20]

Ester cleavage in an aprotic medium has been studied by several groups.[21−24] For example, Nicolaou[25] utilized toxic trimethyltin hydroxide in large excess and elevated reaction temperatures. Laganis[26] and Vinković[27] employed potassium and sodium trimethylsilanolates for the hydrolysis of methyl esters and acyl chlorides. These conditions have been successfully applied in the synthesis of antifungal agent FR-9000848[28] and angiotensin II antagonist telmisartan[29] and in the large-scale production of the RAR-γ agonist BMS-270394.[30]

Our group has described the first example of LRO employing silanolates.[31] We used 2 equiv of (TMS)ONa to open and to induce the rearrangement of epimeric iodolactones **2**, arriving from aucubin (**1**) as shown in Scheme 1. Basicity and

Scheme 1. (TMS)ONa-Induced Rearrangement of Iodolactones 2 to Diastereoselectively Enriched (1*S*,4*R*,5*R*,6*R*)-Bicyclo[3.1.0]hexene (3)



nucleophilicity of (TMS)ONa were demonstrated in the dynamic epimerization at the α-position of lactones **2**, giving thermodynamically favored (1*S*,4*R*,5*R*,6*R*)-bicyclo[3.1.0]-hexene (**3**) with high diastereoselectivity. Following our report, (TMS)OK was found to cleave chiral 1,3-oxazolidinones.[32] However, the use of silanolates for LRO has not yet been a subject of comprehensive studies.

Herein, we describe the scope and the mechanism of mild and selective LRO reactions with (TMS)ONa in high yields. Interestingly, by following the reactions with ^{1}H and ^{13}C NMR,

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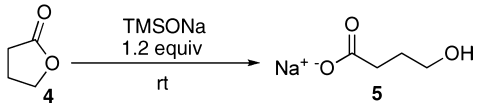
we have found that NaOH present as an impurity accelerates LRO. To demonstrate the potential of our method, we have applied it to chemoselective ring-opening of highly stable natural secoiridoid lactones with various sensitive chemical functions.

RESULTS AND DISCUSSION

To define the best possible reaction conditions, we studied the reaction of γ-butyrolactone (**4**) with (TMS)ONa (commercial 1 M solution in CH_2Cl_2) in different solvents at rt. Our results are summarized in Table 1. Complete conversion required 1.2 equiv of (TMS)ONa regardless of the solvent (compare entries 1 and 3 with entries 2 and 4). In THF and CH_2Cl_2, the sodium salt **5** precipitated and could be isolated by simple filtration of the crude. In contrast, **5** at 0.2 M was completely soluble in DMSO. In aprotic polar solvents (DMF or DMSO), the LRO reaction was somewhat accelerated (entries 5 and 6). Under the employed conditions, for all substrates investigated, the instability of trimethylsilyl ether and/or ester did not permit their detection (^{1}H and ^{13}C NMR).

Table 1. LRO of γ-Butyrolactone ([4] = 0.2 M) with (TMS)ONa (1 M, CH_2Cl_2) in Different Solvents at rt



4 5

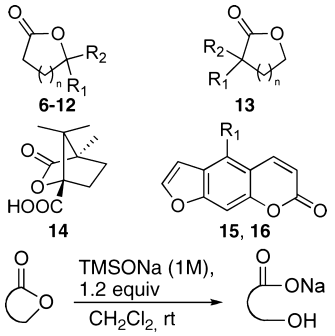
entry	solvent	time (h)	(TMS)ONa[a] (equiv)	conversion (^{1}H NMR) (%)	isolated yield (%)
1	THF	6	1.0	87	74
2	THF	6	1.2	100	83
3	CH_2Cl_2	4	1.0	90	75
4	CH_2Cl_2	4	1.2	100	85
5	DMSO-d_6	3	1.2	100	not isolated[b,c]
6	DMF-d_7	3	1.2	100	not isolated[c]

[a](TMS)ONa contains approximately 10% NaOH. [b]Partial deuteration at C2 was observed by ^{1}H NMR. [c]PhCl is the internal reference.

We then turned to the primary lactones: δ-lactone **8**, ε-lactone **11**, and 15-pentadecanolactone **12** and the secondary lactones: β-lactone **6**, γ-lactone **7**, and δ-lactones **9** and **10** (Table 2). Except for **6**, which polymerized, all other lactones were easily converted into the corresponding hydroxy carboxylate salts in high yields (75−86%) regardless of the substitution and ring size. Encouraged by these results, we tested sterically hindered 2,2-dimethylbutyrolactone (**13**) and 1(*S*)-camphanic acid (**14**). The corresponding hydroxy carboxylic acid of *gem*-dimethyl lactone **13** experiences the Thorpe−Ingold effect and cyclizes readily. However, under standard conditions, **13** gave hydroxy carboxylate **23** in 86% yield, whereas the lactone **14** furnished a similar yield of **24** (82%). Finally, the natural furanocoumarins psoralen (**15**) and bergapten (**16**) with a rigid benzopyranone unit were transformed without *E*/*Z*-isomerization into (*Z*)-**25** (89%) and (*Z*)-**26** (84%), respectively.

The ^{1}H NMR studies of LRO reaction with γ-butyrolactone (**4**) were conducted in DMSO-d_6, the only solvent that solubilizes the reactants and hydroxy acid salt **5** ([**4**] ≤ 0.1 M). The hydroxy acid **5** does not contain the TMS group and is partially deuterated at the α-position (Table 1, entry 5). The major coproducts of the reaction are (TMS)OH(D) and $(TMS)_2O$ in a 1/9 ratio. The latter arises from the reaction (TMS)ONa + (TMS)OH(D) → NaOH(D) + $(TMS)_2O$.[33,34] (TMS)OH(D) can be formed either in the reaction with traces of water present in the reactants and solvent or by the enolization of lactone **4**. The quantity of water in **4** was established as 5 mol % and that of dry DMSO-d_6 as 8−16 mol % with regard to **4**. With progress of the reaction, the chemical shift of the averaged signal of (TMS)ONa and (TMS)OH(D) varied to become that of pure (TMS)OH(D).[35] The solution of (TMS)ONa also contains small amounts of $(TMS)_2O$ as established by ^{1}H NMR and NaOH (5−22 mol % with regard to **4**) as measured by back-titration.[36]

Table 2. Variation of Ring Sizes and Substitutions in LRO Using (TMS)ONa (1 M, CH_2Cl_2)



entry	substrate	n	R_1	R_2	product (yield, %)
1	**6**	0	Me	H	(polymerization)
2	**4**	1	H	H	**5** (85)
3	**7**	1	Me	H	**17** (75)
4	**8**	2	H	H	**18** (77)
5	**9**	2	Me	H	**19** (86)
6	**10**	2	$(CH_2)_6CH_3$	H	**20** (82)
7	**11**	3	H	H	**21** (80)
8	**12**	12	H	H	**22**[a] (78)
9	**13**	1	Me	Me	**23**[b] (86)
10	**14**				**24** (82)
11	**15**		H		**25** (89)
12	**16**		OMe		**26** (84)

[a]Isolated as the hydroxy acid. [b](TMS)ONa 2.4 equiv, reflux.

Scheme 2 shows the $B_{Al}2$ and $B_{Ac}2$ mechanistic pathways for LRO. For ester cleavage with (TMS)ONa, the $B_{Al}2$ mechanism was proposed via the nucleophilic attack of silanolate on the methylene group (S_N2 type).[27] LRO reaction may follow the $B_{Ac}2$ pathway proceeding through an addition of (TMS)ONa to the carbonyl of the lactone, leading to the formation of the trimethylsilyl ester **28** after ring-opening (Scheme 2).

Scheme 2. $B_{Al}2$ and $B_{Ac}2$ Pathways of LRO with (TMS)ONa

The mechanism of LRO with (TMS)ONa was elucidated by kinetic studies using γ-butyrolactone (**4**) or γ-valerolactone (**7**) under pseudo-first-order conditions by ^{1}H NMR in DMSO-d_6. The fact that the reaction rate of LRO with **4** using NaOH instead of (TMS)ONa considerably decreases (see the Supporting Information) confirms that (TMS)ONa is responsible for lactone-opening. The rate law of the LRO of **4** was

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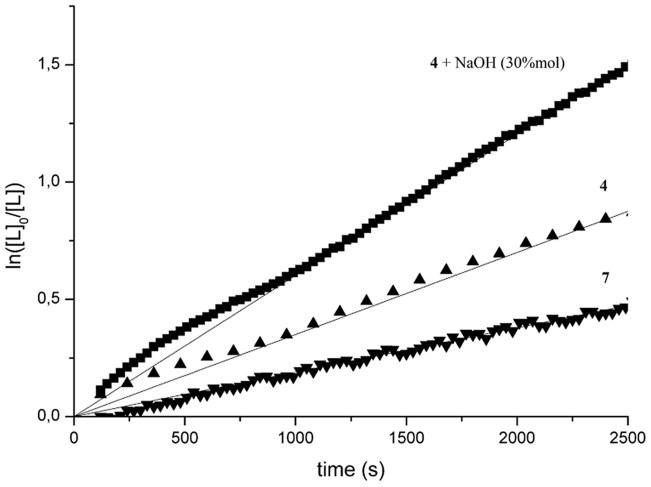
first-order in both reactants (TMS)ONa and **4**: k((TMS)ONa) = 4.8 × 10^{-3} ± 0.2 × 10^{-3} M^{-1} s^{-1} and k(**4**) = 4.6 × 10^{-3} ± 0.1 × 10^{-3} M^{-1} s^{-1} at 25 °C. The half-life of secondary lactone **7** in LRO reaction conditions ($\tau_{1/2}$ = 3670 ± 190 s) is nearly the same as that of primary lactone **4** ($\tau_{1/2}$ = 1980 ± 110 s) (Figure 1). This is inconsistent with a $B_{Al}2$ mechanism in which



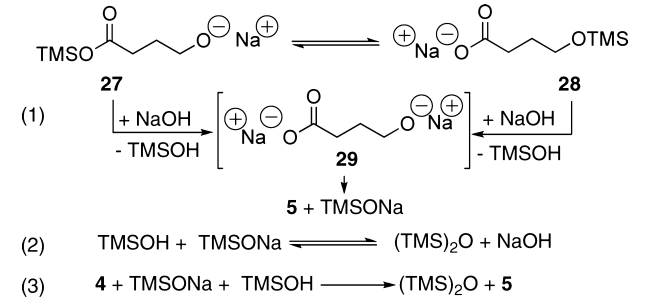
Substrate	k/10^{-4}mol^{-1}Ls^{-1}	$t_{1/2}$/s
4	3.5±0.2	1980±110
7	1.9±0.1	3670±190
4 + NaOH(30%)	6.0±0.2	1150±40

Figure 1. Initial rates interpolated as pseudo-first-order for LRO of γ-valerolactone (**7**), γ-butyrolactone (**4**), and **4** + NaOH (30 mol %). [lactone]$_o$ = 0.09 M, [(TMS)ONa]$_o$ = 0.09 M, and t = 20 °C.

(TMS)ONa would have displaced the CH(Me)−OCO group of **7** and the CH_2−OCO group of **4**. Because of the steric hindrance in the secondary lactone **7**, the latter is expected to react at least 1000 times slower than **4**.[37] The order of the reaction (TMS)ONa + **4** and this finding are consistent with a $B_{Ac}2$ mechanism, with the rate-determining step being the addition of (TMS)ONa to the carbonyl of the lactone.

The cleavage of the Si group can be interpreted in terms of the mechanism shown in Scheme 3. Intermediate **27** generated

Scheme 3. TMS Group Cleavage in LRO with (TMS)ONa



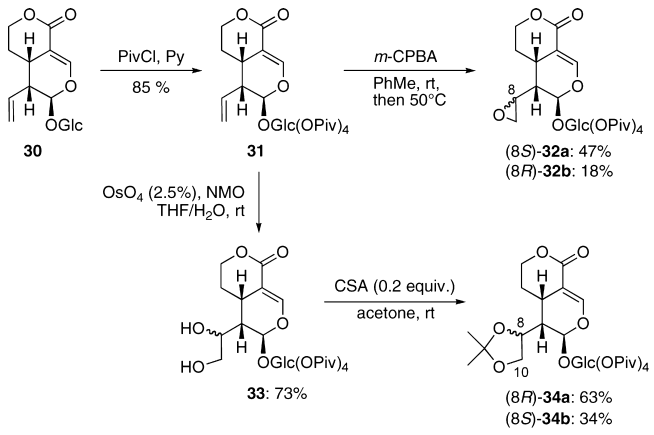
by LRO undergoes a fast transfer of the TMS group from the trimethylsilyl ester to alkoxide (p$K_{a,DMSO}$(RCOOH) = 12.6[38] and p$K_{a,DMSO}$(RCH_2OH) = 28[39]) and produces the more stable trimethylsilyl ether **28**. In the presence of NaOH, ester **27** or ether **28** may be cleaved into **29** + (TMS)OH, which equilibrates with 4-hydroxybutyrate (**5**) and (TMS)ONa (Scheme 3). The small quantity of NaOH remains enough to interfere with the mechanism. The consumption of NaOH during the reaction shifts equilibrium 2 toward $(TMS)_2O$, and these two compounds were observed as major coproducts by ^{1}H NMR.

To further confirm the proposed mechanism, we measured the initial rate interpolated as pseudo-first-order for LRO of **4** + NaOH (30 mol %) and compared it to the rates for **4** and **7** employing previously described conditions (Figure 1). The addition of 30 mol % NaOH increased the rate of LRO for **4** by a factor of 1.8 ($\tau_{1/2}$ = 1150 ± 40 s), suggesting the accelerating role of NaOH. The existence of the equilibria described in eqs 1 and 3 is confirmed by the difference in the ratio [$(TMS)_2O$]/([(TMS)ONa] + [(TMS)OH]), 1.7 vs 7.7 for the LRO of **4** without and with NaOH (30 mol %) after 1 h and 40 min.

Some iridoids are abundant in nature and can be extracted readily from various plants.[3] We have used them as chiral green bioresources. Indeed, they constitute valuable starting materials for the synthesis of bioactive compounds.[31,40−43] Our group has developed new chiral scaffolds and building blocks starting from aucubin (**1**), leading to the construction of new heterocyclic systems via their pyran ring contraction or expansion, generating a wide skeletal and chemodiversity. In particular, this has allowed us to prepare new amino acids,[44] enoxysilanes,[43] and aminocyclopentanol glucosidase inhibitors.[31] We also have obtained a new series of cytotoxic cyclopentenone glucosides[45,46] and polyaminoiridoids structurally related to aminoside antibiotics.[47]

To enlarge the scope of our original chiral building blocks available from renewable phytomaterial,[48−50] we applied our LRO method to open lactones of secoiridoids with a fully protected glycosyl moiety. Except for the semisynthesis of alkaloid indolomonoterpenes,[51−57] secoiridoids were rarely used as chiral starting materials.[58−61] The lactone ring of pyrano[3,4-*c*]pyranone is known to be very stable, and thus, its LRO is difficult.[48−50,53] Sweroside (**30**) was readily extracted from *Lonicera tatarica* (Caprifoliaceae).[52] Its glucoside unit was fully protected in 85% yield (**31**, Scheme 4). Stereoisomers **32a**

Scheme 4. Syntheses of Sweroside Derivatives 31−34



and **32b** were obtained by epoxidation[53,58,59] of **31** with *m*-CPBA in 47% and 18% yields, respectively. The inseparable mixture of diols **33a** and **33b** (8*R*/8*S*) was obtained in 73% yield by catalytic dihydroxylation of **31** with OsO_4 (2.5 mol %)/NMO.[59] Acetonides **34a** and **34b** were isolated in 63% and 34% yields, respectively, after flash chromatography.

To demonstrate the utility of (TMS)ONa for LRO, NaOH, LiOH, MeONa, and Me_3SnOH were tested. NaOH or LiOH

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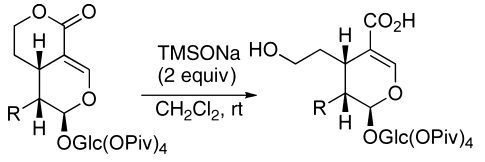
cleaved the ester protections of **31** without opening the lactone moiety. With MeONa, **31** underwent a concomitant 1,4-addition of MeOH to its ene ester moiety, and pivaloyl ester groups were also cleaved. However, an excess of Me_3SnOH (10 equiv) in 1,2-DCE at 80 °C led to less than 30% conversion to hydroxy acid **35** after 24 h. When we applied our new LRO methodology, no concurrent reactions were observed. The lactone **31** was chemoselectively opened with 2 equiv of (TMS)ONa in CH_2Cl_2 at rt. After neutralization with SiO_2, perpivaloylsecologanol **35** was isolated in 88% yield (Table 3, entry 1).

Table 3. LRO of Sweroside Derivatives 31−34 with (TMS)ONa

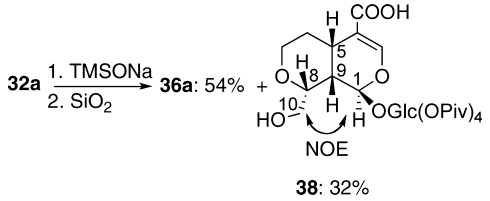


Entry	Substrate	R	Time (h)	Product (yield %)
1	**31**		12	**35** (88)
2	**32a**		24	(8*S*)-**36a** (86)[a]
3	**32b**		48	(8*R*)-**36b** (87)
4	**33**		48	No reaction
5	**34a**		39	(8*R*)-**37a** (65)
6	**34b**		24	(8*S*)-**37b** (84)

[a]The yield was evaluated by ^1H NMR.

To our delight, the LRO reactions of the sweroside derivatives **32**−**34** with (TMS)ONa were also highly chemoselective (Table 3). The reaction of **32b** (entry 3, 48 h) proceeded in 87% yield, and epimer **32a** was converted into **36a** in 86% yield without epoxide ring-opening. The ^1H NMR of the crude **36a** confirmed high selectivity of the reaction. However, during the purification on silica, **36a** was partially rearranged into **38** resulting from a favorable intramolecular nucleophilic attack of alkoxide on C8 of its epoxide moiety (Scheme 5). The structure of the tetrahydropyran ring was

Scheme 5. Formation of Morroniside-Type Structure 38



established by the $^3J_{H-H}$ coupling constant between the H_5, H_6, H_8, and H_9 protons. In particular, the relative configuration of C8 was given by $^3J_{H_8-H_9} = {}^3J_{H_9-H_5} = 6.0$ Hz, which proved the synperiplanar stereochemistry of protons H_8, H_9, and H_5. Further NOESY correlation between H_{10} and H_1 confirmed the 8*R* configuration. The reaction of (TMS)ONa with acetonides **34a** and **34b** led to the hydroxy acids **37a** (65%) and **37b** (84%) (entries 5 and 6). The lower yield for the formation of (8*S*)-**37b** is probably due to steric interactions between the acetonide and pyrano[3,4-*c*]pyranone parts. Protection of diol **33** is necessary as the latter compound did not undergo LRO with a 5-fold excess of (TMS)ONa (Table 3, entry 4).

In conclusion, we have developed a mild and chemoselective LRO reaction that uses (TMS)ONa in an aprotic solvent. Kinetic studies using NMR confirmed a $B_{Ac}2$ mechanism of the reaction. NaOH present as an impurity has an important role as it increases the rate of LRO. This chemoselective method has been efficiently applied to LRO of complex natural products, providing the hydroxy acids in high yields. In particular, new secoiridoid-based chiral building blocks have been obtained by that chemistry. Further studies will explore their use in semisynthesis of compounds with biological interest.

EXPERIMENTAL SECTION

General Information. Optical rotations were measured (*c*, g/L). NMR spectra were recorded on 400 and/or 300 MHz spectrometers, and chemical shifts are expressed in parts per million downfield from TMS. When necessary, all structures of the novel compounds were ensured and the signals unambiguously assigned by 2D NMR techniques: $^1H-^1H$ COSY, $^1H-^1H$ NOESY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC. These experiments were performed using standard microprograms. Chemical shifts are corrected to δ_H 7.26 for $CDCl_3$, δ_H 4.79 for D_2O, or δ_H 2.50 for DMSO-d_6 as the internal reference and to δ_C 77.00 for $CDCl_3$ or δ_C 39.52 for DMSO-d_6 as the internal reference. Splitting patterns in the ^1H NMR spectra are designated as s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin = quintuplet, sext = sextuplet, m = multiplet, and br = broad. DMSO-d_6 was dried over calcium hydride, distilled, and stored over 4 Å molecular sieves. ESI-MS and HR-ESI-MS were performed on QTOF apparatuses equipped with an ESI-Z spray source. TLC was performed on silica gel 60 F254 aluminum sheets using vanillin/H_2SO_4 as the spray reagent. Column chromatographies were conducted using silica gel [20−45 or 35−70 μm (flash)] with an overpressure of 300 mbar. Dichloromethane was dried over calcium hydride and distilled. Yields refer to chromatographically and spectroscopically pure compounds. Trivial nomenclature of iridoids was employed. (TMS)ONa was purchased as a 1 M solution in dichloromethane.

General Procedure GP01 for Lactone Ring-Opening of Commercial Lactone Exemplified by the Synthesis of Sodium 4-Hydroxybutyrate (5). To a solution of γ-butyrolactone (**4**) (86 mg, 1.0 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) was added a commercial solution of (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv). The mixture was stirred under a nitrogen atmosphere at room temperature for 4 h, filtered, and washed by pentane (4 × 20 mL). The white solid was dried in vacuo to furnish **5** (107 mg, 85%). ^1H NMR (400 MHz, D_2O): δ 3.54 (2H, t, $^3J_{4-3}$ = 6.5 Hz, H_4), 2.18 (2H, t, $^3J_{2-3}$ = 6.5 Hz, H_2), 1.74 (2H, quint, $^3J_{3-2} = {}^3J_{3-4}$ = 6.5 Hz, H_3); ^{13}C NMR (100 MHz, D_2O): δ 183.1 (C1), 61.4 (C4), 33.9 (C2), 28.3 (C3); IR (ATR): ν 3317, 2960, 1555 (COO^-), 1407, 1065, 1053, 1014, 946, 920, 888, 685 cm^{-1}; MS (ESI^-): *m*/*z* 103 [M − Na]$^-$. HRMS (ESI^-): *m*/*z* for $C_4H_7O_3$ [M − Na]$^-$, calcd 103.0401, found 103.0401. Spectral data were consistent with the literature.[62−64]

Sodium 4-Hydroxypentanoate (17). General procedure GP01 was applied using γ-valerolactone (**7**) (100 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 6 h. The title compound **17** was obtained as a white solid (105 mg, 75%). ^1H NMR (300 MHz, D_2O): δ 3.75 (1H, sext, $^3J_{4-5} = {}^3J_{4-3}$ = 6.5 Hz, H_4), 2.19 (1H, dt, $^2J_{2a-2b}$ = 20.0 Hz, $^3J_{2-3}$ = 7.5 Hz, H_{2a}), 2.14 (1H, dt, $^2J_{2b-2a}$ = 20.0 Hz, $^3J_{2-3}$ = 7.5 Hz, H_{2b}), 1.64 (2H, td, $^3J_{3-2}$ = 7.5 Hz, $^3J_{3-4}$ = 6.5 Hz, H_3), 1.11 (3H, d, $^3J_{5-4}$ = 6.5 Hz, H_5); ^{13}C NMR (75 MHz, D_2O): δ 183.2 (C1), 67.5 (C4), 34.6 (C3), 33.8 (C2), 21.5 (C5); IR (ATR): ν 2947, 1565 (COO^-), 1439, 1413, 1237, 1130, 1072, 946, 818, 737, 665 cm^{-1}; MS (ESI^-): *m*/*z* 117 [M − Na]$^-$. HRMS (ESI^-): *m*/*z* for $C_5H_9O_3$ [M − Na]$^-$, calcd 117.0557, found 117.0556. Spectral data were consistent with the literature.[65]

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Sodium 5-Hydroxypentanoate (18). General procedure GP01 was applied using δ-valerolactone (**8**) (100 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 6 h. The title compound **18** was obtained as a white solid (107 mg, 77%). ^{1}H NMR (300 MHz, D_2O): δ 3.57 (2H, t, $^3J_{5-4}$ = 6.5 Hz, H_5), 2.16 (2H, t, $^3J_{2-3}$ = 6.5 Hz, H_2), 1.61−1.47 (4H, m, H_3, H_4); ^{13}C NMR (75 MHz, D_2O): δ 183.7 (C1), 61.4 (C5), 37.1 (C2), 31.1 (C4), 22.1 (C3); IR (ATR): ν 3432, 2941, 1734, 1561 (COO^-), 1444, 1420, 1249, 1166, 1064, 922, 838 cm^{-1}; MS (ESI^-): *m*/*z* 117 $[M - Na]^-$. HRMS (ESI^-): *m*/*z* for $C_5H_9O_3$ $[M - Na]^-$, calcd 117.0557, found 117.0558. Spectral data were consistent with the literature.[67,68]

Sodium 5-Hydroxyhexanoate (19). General procedure GP01 was applied using δ-caprolactone (**9**) (114 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 16 h. The title compound **19** was obtained as a white solid (132 mg, 86%). ^{1}H NMR (300 MHz, D_2O): δ 3.80 (1H, sext, $^3J_{5-4}$ = $^3J_{5-6}$ = 6.0 Hz, H_5), 2.16 (2H, t, $^3J_{2-3}$ = 7.0 Hz, H_2), 1.67−1.35 (4H, m, H_3, H_4), 1.13 (3H, d, $^3J_{6-5}$ = 6.0 Hz, H_6); ^{13}C NMR (75 MHz, D_2O): δ 183.7 (C1), 67.6 (C5), 37.6 (C2), 37.3 (C4), 22.0 (C3), 21.7 (C6); IR (ATR): ν 3336, 2964, 2930, 1705, 1559 (COO^-), 1404, 1373, 1252, 1130, 1088, 1027, 946, 883, 749 cm^{-1}; MS (ESI^-): *m*/*z* 131 $[M - Na]^-$. HRMS (ESI^-): *m*/*z* for $C_6H_{11}O_3$ $[M - Na]^-$, calcd 131.0714, found 131.0716.

Sodium 5-Hydroxydodecanoate (20). General procedure GP01 was applied using δ-dodecalactone (**10**) (114 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 16 h. The title compound **20** was obtained as a white solid (195 mg, 82%). ^{1}H NMR (300 MHz, D_2O): δ 3.54 (1H, tt, $^3J_{5-4}$ = 7.0 Hz, $^3J_{5-6}$ = 5.0 Hz, H_5), 2.06 (2H, t, $^3J_{2-3}$ = 7.5 Hz, H_2), 1.61−1.07 (16 H, m, H_3, H_4, H_6, H_7, H_8, H_9, H_{10}, H_{11}), 0.74 (3H, t, $^3J_{12-11}$ = 7.0 Hz, H_{12}); ^{13}C NMR (75 MHz, D_2O): δ 183.7 (C1), 71.4 (C5), 37.4 (C2), 35.8, 35.7, 31.1, 28.7, 28.3, 24.6, 22.0, 21.9 (8 CH_2), 13.3 (C12); IR (ATR): ν 3310, 2954, 2920, 2848, 1704, 1564 (COO^-), 1459, 1409, 1130, 1094, 912, 887, 723 cm^{-1}; MS (ESI^-): *m*/*z* 215 $[M - Na]^-$. HRMS (ESI^-): *m*/*z* for $C_{12}H_{23}O_3$ $[M - Na]^-$, calcd 215.1653, found 215.1651.

Sodium 6-Hydroxyhexanoate (21). General procedure GP01 was applied using ε-caprolactone (**11**) (114 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 16 h. The title compound **21** was obtained as a white solid (123 mg, 80%). ^{1}H NMR (300 MHz, D_2O): δ 3.54 (2H, t, $^3J_{6-5}$ = 6.5 Hz, H_6), 2.13 (2H, t, $^3J_{2-3}$ = 7.5 Hz, H_2), 1.56−1.45 (4H, m, H_3, H_5), 1.33−1.23 (2H, m, H_4); ^{13}C NMR (75 MHz, D_2O): δ 184.0 (C1), 61.6 (C6), 37.4 (C2), 31.0 (C5), 25.5 (C3), 24.9 (C4); IR (ATR): ν 3303, 2939, 1558 (COO^-), 1443, 1416, 1253, 1071, 1049, 958, 840 cm^{-1}; MS (ESI^-): *m*/*z* 131 $[M - Na]^-$. HRMS (ESI^-): *m*/*z* for $C_6H_{11}O_3$ $[M - Na]^-$, calcd 131.0714, found 131.0712.

15-Hydroxypentanoic Acid (22). To a solution of 15-pentadecanolactone (**12**) (240 mg, 1.0 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) was added a commercial solution of (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv). The mixture was stirred at room temperature for 16 h, then diluted with CH_2Cl_2 (15 mL), and neutralized with an aqueous solution of HCl (10%) at 0 °C. The organic layer was washed by water (2 × 20 mL) and brine (1 × 20 mL), dried over $MgSO_4$, and evaporated in vacuo to give **22** as a white solid (201 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (2H, t, $^3J_{15-14}$ = 6.0 Hz, H_{15}), 2.07 (2H, t, $^3J_{2-3}$ = 7.5 Hz, H_2), 1.44−1.23 (4H, m, H_3, H_{14}), 1.14−0.94 (20H, m, H_4, H_5, H_6, H_7, H_8, H_9, H_{10}, H_{11}, H_{12}, H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.9 (C1), 63.1 (C15), 33.9 (C2), 32.7 (C14), 29.53, 29.51, 29.48, 29.45, 29.37, 29.34, 29.25, 29.16, 28.99, 25.7, 24.7 (C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13); IR (ATR): ν 2915, 2849, 1737, 1691, 1470, 1413, 1221, 1197, 1178, 1058, 971, 718 cm^{-1}; MS (ESI^-): *m*/*z* 257 $[M^- - H]$. HRMS (ESI^-): *m*/*z* for $C_{15}H_{29}O_3$ $[M^- - H]$, calcd 257.2122, found 257.2118. Spectral data were consistent with the literature.[66,67]

Sodium 4-Hydroxy-2,2-dimethylbutanoate (23). General procedure GP01 was applied using α,α-dimethyl-γ-butyrolactone (**13**) (114 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 12 h. The title compound **23** was obtained as a white powder (133 mg, 86%). ^{1}H NMR (400 MHz, D_2O): δ 3.47 (t, $^3J_{3-4}$ = 7.5 Hz, 2H, H_4), 1.63 (t, $^3J_{3-4}$ = 7.5 Hz, 2H, H_3), 0.99 (s, 6H, 2 × CH_3). ^{13}C NMR (100.6 MHz, D_2O): δ 187.1 (C1), 59.2 (C4), 42.4 (C3), 41.9 (C2), 25.7 (2 × CH_3). IR (ATR): ν 3330, 2980, 2950, 2900, 2920, 1660, 1520, 1400, 1070. MS (ESI): *m*/*z* $[M^+]$ 154. Mp: 180.2−183.5 °C. HRMS (ESI): *m*/*z* for $C_6H_{11}NaO_3$, calcd $C_6H_{12}NaO_3$ $[M + H]^+$ 155.0684, found 155.0681.

1,3-Disodium (1*S*,3*R*)-1-Hydroxy-2,2,3-trimethylcyclopentane-1,3-dicarboxylate (24). To a solution of camphanic acid (**14**) (198 mg, 1.0 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) was added a commercial solution of (TMS)ONa (1 M) in CH_2Cl_2 (2.4 mL, 2.4 mmol, 2.4 equiv). The mixture was stirred at reflux for 6 h and then diluted at rt with CH_2Cl_2 (15 mL). To the solution was added water (20 mL), and the solution was washed by CH_2Cl_2 (2 × 20 mL). The water was evaporated under reduced pressure to give **22** as a white solid (213 mg, 78%). $[\alpha]_D$ = −25.2 (*c* = 3.0 in H_2O); ^{1}H NMR (400 MHz, D_2O): δ 2.53 (ddd, $^2J_{5a-5b}$ = 14.0 Hz, $^3J_{5a-4a}$ = 9.0 Hz, $^3J_{5a-4b}$= 5.0 Hz, 1H, H_{5a}), 2.17 (ddd, $^2J_{4a-4b}$ = 13.5 Hz, $^3J_{4a-5a}$ = 9.0 Hz, $^3J_{4a-5b}$ = 3.5 Hz, 1H, H_{4a}), 1.66 (ddd, $^2J_{5a-5b}$ = 14.0 Hz, $^3J_{5b-4b}$ = 9.0 Hz, $^3J_{5b-4a}$ = 3.5 Hz, 1H, H_{5b}), 1.50 (ddd, $^2J_{4a-4b}$ = 13.5 Hz, $^3J_{4b-5b}$ = 9.0 Hz, $^3J_{4b-5a}$ = 5.0 Hz, 1H, H_{4b}), 0.96 (s, 3H, CH_3−C(3)), 0.86 (s, 3H, CH_3−C(2)), 0.75 (s, 3H, CH_3−C(2)). ^{13}C NMR (100.6 MHz, D_2O): δ 187.9; 180.5 (C1, C2); 90.3 (C1); 57.0 (C3); 49.1 (C2); 35.5; 35.1 (C4, C5); 23.5 (CH_3−C(3)); 21.7 (CH_3−C(2)); 19.2 (CH_3−C(2)). IR (ATR): ν 3450, 3030, 3020, 3000, 2950, 2240, 2120, 1980, 1740, 1550, 1430, 1670, 1230, 1220, 1070, 900. MS (ESI): *m*/*z* $[M + Na]^+$ 283. Mp: 311−314 °C. HRMS (ESI): *m*/*z* for $C_{10}H_{14}Na_2O_5$, calcd $[M + H]^+$ $C_{10}H_{15}Na_2O_5$ 261.0709, found 261.0710.

Sodium (2*Z*)-3-(6′-Hydroxy-1′-benzofuran-5′-yl)prop-2-enoate (25). General procedure GP01 was applied using psoralen (**15**) (186 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 12 h. Compound **25** was obtained as a brown powder (201 mg, 89%). ^{1}H NMR (400 MHz, D_2O): δ 7.43 (br s, 1H, $H_{4'}$), 7.36 (d, $^3J_{1'-2'}$ = 2.5 Hz, 1H, $H_{1'}$), 6.71 (d, $^3J_{2-3}$ = 12.5 Hz, $^5J_{7'-3}$ = 0.5 Hz, 1H, H_3), 6.62 (br d, $^5J_{7'-3}$ = 0.5 Hz, $^5J_{7'-2'}$ = 1 Hz, 1H, $H_{7'}$), 6.59 (dd, $^3J_{1'-2'}$ = 2.5 Hz, $^5J_{2'-7'}$ = 1 Hz, 1H, $H_{2'}$), 5.82 (d, $^3J_{2-3}$ = 12.5 Hz, 1H, H_2). ^{13}C NMR (100.6 MHz, D_2O): δ 178.2 (C1), 163.1 (C8′), 157.0 (C6′), 142.5 (C1′), 130.0 (C3), 123.4 (C3′), 123.3 (C2), 120.0 (C4′), 115.4 (C5′), 106.5 (C2′), 99.3 (C7′). IR (ATR): ν 3190, 3030, 3020, 2950, 2240, 2150, 1740, 1580, 1550, 1420, 1350, 1220, 1160, 1030 cm^{-1}; UV (H_2O): λ_{max} (log ε) 201 nm (1.55), 245 (1.31), 299 (0.64); MS (ESI): *m*/*z* $[M + Na]^+$ 249. HRMS (ESI): *m*/*z* for $C_{11}H_7NaO_4$, calcd $[M + H]^+$ $C_{11}H_8NaO_4$ 227.0314, found 227.0317.

Sodium (2*Z*)-3-(6′-Hydroxy-4′-methoxy-1′-benzofuran-5′-yl)prop-2-enoate (26). General procedure GP01 was applied using bergapten (**16**) (216 mg, 1.0 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (1.2 mL, 1.2 mmol, 1.2 equiv) for 12 h. Compound **26** was obtained as a brown powder (214 mg, 84%). ^{1}H NMR (400 MHz, D_2O): δ 7.32 (d, $^3J_{1'-2'}$ = 2.5 Hz, 1H, $H_{1'}$), 6.79 (br d, $^3J_{1'-2'}$ = 2.5 Hz, 1H, $H_{2'}$), 6.46 (d, $^3J_{2-3}$ = 12.5 Hz, 1H, H_3), 6.38 (br s, 1H, $H_{7'}$), 5.91 (d, $^3J_{2-3}$ = 12.5 Hz, 1H, H_2), 3.82 (s, 3H, OCH_3). ^{13}C NMR (100.6 MHz, D_2O): δ 176.9 (C1), 164.5 (C8′), 157.7 (C6′), 149.7 (C4′), 141.0 (C1′), 129.0 (C3); 126.7 (C2); 114.6 (C5′); 106.4 (C3′), 104.8 (C2′), 94.7 (C7′); 59.0 (OCH_3). IR (ATR): ν 3290, 3020, 3005, 2970, 2240, 2130, 1740, 1730, 1550, 1370, 1220, 1160, 970. UV: λ_{max} (log ε) 198 nm (1.44), 251 (1.26), 308 (0.63); MS (ESI): *m*/*z* $[M^+]$ 256 $[2M + Na]^+$ 535. HRMS (ESI): *m*/*z* for $C_{12}H_9NaO_5$, calcd $[M + Na]^+$ $C_{12}H_9Na_2O_5$ 279.0239, found 279.0235.

Perpivaloylsweroside (31). To a solution of sweroside (**30**) (4.85 g, 13.5 mmol, 1 equiv) in a mixture of anhydrous pyridine and CH_2Cl_2 (90 mL/90 mL), cooled with an ice bath, was added pivaloyl chloride (19.8 mL, 162 mmol, 12 equiv) followed by 4-DMAP (992 mg, 8.12 mmol, 0.6 equiv). The mixture was agitated at room temperature for 14 days and then quenched with 10 g of ice and 30 mL of water. The resulting mixture was extracted by CH_2Cl_2 (3 × 70 mL), and the combined organic layers were neutralized at 0 °C by addition of aqueous HCl (10%) until the pH of the aqueous layer remained acidic (pH 2). The organic layer was then washed by water (2 × 50 mL) and brine (3 × 50 mL), dried over $MgSO_4$, filtered, and

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evaporated under reduced pressure. The crude was then purified by flash chromatography (cyclohexane/AcOEt, 99/1 to 90/10) to give **31** (7.97 g, 11.5 mmol, 85%) as a white powder. $[\alpha]_D = -76.5$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, d, $^4J_{3-5} = 2.5$ Hz, H_3), 5.43 (1H, dt, $^3J_{8-10a} = 17.5$ Hz, $^3J_{8-10b} = {}^3J_{8-9} = 10.0$ Hz, H_8), 5.35 (1H, d, $^3J_{1-9} = 1.5$ Hz, H_1), 5.34 (1H, t, $^3J_{3'-2'} = {}^3J_{3'-4'} = 9.5$ Hz, $H_{3'}$), 5.31−5.22 (2H, m, H_{10}), 5.10 (1H, t, $^3J_{4'-3'} = {}^3J_{4'-5'} = 9.5$ Hz, $H_{4'}$), 5.02 (1H, dd, $^3J_{2'-3'} = 9.5$ Hz, $^3J_{2'-1'} = 8.0$ Hz, $H_{2'}$), 4.91 (1H, d, $^3J_{1'-2'} = 8.0$ Hz, $H_{1'}$), 4.42 (1H, dt, $^2J_{7a-7b} = 11.5$ Hz, $^3J_{7a-6b} = {}^3J_{7a-6a} = 3.0$ Hz, H_{7a}), 4.21 (1H, ddd, $^2J_{7b-7a} = 11.5$ Hz, $^3J_{7a-6a} = 8.5$ Hz, $^3J_{7a-6b} = 6.0$ Hz, H_{7b}), 4.17 (1H, dd, $^2J_{6'a-6'b} = 12.5$ Hz, $^3J_{6'a-5'} = 2.0$ Hz, $H_{6'a}$), 4.09 (1H, dd, $^2J_{6'b-6'a} = 12.5$ Hz, $^3J_{6'b-5'} = 6.0$ Hz, $H_{6'b}$), 3.80 (1H, ddd, $^3J_{5'-4'} = 9.5$ Hz, $^3J_{5'-6'b} = 6.0$ Hz, $^3J_{5-6a'} = 2.0$ Hz, $H_{5'}$), 2.86−2.76 (1H, m, H_5), 2.62 (1H, ddd, $^3J_{9-8} = 10.0$ Hz, $^3J_{9-5} = 5.5$ Hz, $^3J_{9-1} = 1.5$ Hz, H_9), 1.73−1.64 (2H, m, H_6), 1.19, 1.13, 1.09, 1.08 (36H, 4s, $COC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 177.1, 176.8, 176.6 (4C, $COC(CH_3)_3$), 164.8 (C11), 152.0 (C3), 131.1 (C8), 120.9 (C10), 105.0 (C4), 95.9 (C1′), 95.7 (C1), 72.6 (C5′), 72.1 (C3′), 70.8 (C2′), 68.2 (C7), 68.1 (C4′), 61.9 (C6′), 42.2 (C9), 39.8, 38.7, 38.6 (4C, $C(CH_3)_3$), 27.5 (C5), 27.3, 27.2, 27.1, 27.0 (4C, $C(CH_3)_3$), 24.7 (C6); IR (ATR): ν 2972, 1737 (C═O), 1624, 1480, 1275, 1131, 1064, 981, 843, 761 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 242 nm (4.01); MS (ESI$^+$): m/z 717 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{54}O_{13}Na$ [M + Na]$^+$, calcd 717.3456, found 717.3454.

9-((8*S*)-Epoxy)perpivaloylsweroside (32a) and 9-((*R*)-Epoxy)-perpivaloylsweroside (32b). To a solution of **31** (585 mg, 0.842 mmol, 1 equiv) in dry toluene (15 mL), was added *m*-CPBA (207 mg, 0.842 mmol, 1 equiv), and the mixture was stirred at 50 °C for 24 h. Then an additional 2 equiv of *m*-CPBA (414 mg, 1.684 mmol) was added, and the mixture was stirred for 48 h at 50 °C. The reaction was then diluted by CH_2Cl_2 (50 mL) and washed by 5% aqueous NaOH solution (2 × 20 mL) and brine (3 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography (cyclohexane/AcOEt, 80/20) to give, in order of elution, the recovered starting material **31** (57 mg, 10%), the minor compound (*R*)-**32b** as a white solid (108.3 mg, 18%), and compound (*S*)-**32a** as a white solid (278.5 mg, 47%). The absolute configurations of the two diastereoisomers were determined by comparison with the literature.[58]

Major Compound: 9-((8S)-Epoxy)perpivaloylsweroside (32a). $[\alpha]_D = -86.0$ ($c = 0.18$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (1H, d, $^4J_{3-5} = 2.5$ Hz, H_3), 5.69 (1H, d, $^3J_{1-9} = 1.5$ Hz, H_1), 5.35 (1H, t, $^3J_{3'-2'} = {}^3J_{3'-4'} = 9.5$ Hz, $H_{3'}$), 5.10 (1H, t, $^3J_{4'-3'} = {}^3J_{4'-5'} = 9.5$ Hz, $H_{4'}$), 5.01 (1H, br dd, $^3J_{2'-3'} = 9.5$ Hz, $^3J_{2'-1'} = 8.0$ Hz, $H_{2'}$), 4.95 (1H, d, $^3J_{1'-2'} = 8.0$ Hz, $H_{1'}$), 4.48 (1H, dm, $^2J_{7a-7b} = 11.0$ Hz, H_{7a}), 4.24 (1H, m, $^2J_{7a-7b} = 11.0$ Hz, H_{7b}), 4.16−4.11 (2H, m, $H_{6'}$), 3.85−3.77 (1H, m, $H_{5'}$), 2.96−2.88 (1H, m, H_5), 2.86 (1H, br dd, $^2J_{10a-10b} = 5.0$ Hz, $^3J_{10a-8} = 4.0$ Hz, H_{10a}), 2.70 (1H, ddd, $^3J_{8-9} = 9.5$ Hz, $^3J_{8-10a} = 4.0$ Hz, $^3J_{8-10b} = 2.5$ Hz, H_8), 2.55 (1H, dd, $^2J_{10b-10a} = 5.0$ Hz, $^3J_{10b-8} = 2.5$ Hz, H_{10b}), 1.91−1.80 (2H, m, H_6), 1.62 (1H, ddd, $^3J_{9-8} = 9.5$ Hz, $^3J_{9-5} = 5.5$ Hz, $^3J_{9-1} = 1.5$ Hz, H_9), 1.23, 1.14, 1.09, 1.08 (36H, 4s, $COC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 176.9, 176.7, 176.4 (4C, $COC(CH_3)_3$), 164.2 (C11), 152.4 (C3), 104.7 (C4), 96.0 (C1′), 93.8 (C1), 72.5 (C5′), 71.9 (C3′), 70.7 (C2′), 68.1 (C7), 67.8 (C4′), 61.7 (C6′), 48.1 (C8), 47.4 (C10), 40.7 (C9), 38.8, 38.7, 38.6 (4C, $C(CH_3)_3$), 27.1, 27.0 (4C, $C(CH_3)_3$), 26.9 (C5), 24.6 (C6); IR (ATR): ν 2973, 1737 (C═O), 1625, 1480, 1398, 1368, 1271, 1131, 1068, 985, 838, 761 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (4.14), 240 (4.32); MS (ESI$^+$): m/z 733 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{54}NaO_{14}$ [M + Na]$^+$, calcd 733.3400, found 733.3402.

Minor Compound: 9-((8R)-Epoxy)perpivaloylsweroside (32b). $[\alpha]_D = -64.5$ ($c = 0.31$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (1H, d, $^4J_{3-5} = 2.5$ Hz, H_3), 5.47 (1H, d, $^3J_{1-9} = 1.5$ Hz, H_1), 5.35 (1H, t, $^3J_{3'-2'} = {}^3J_{3'-4'} = 9.5$ Hz, $H_{3'}$), 5.11 (1H, t, $^3J_{4'-3'} = {}^3J_{4'-5'} = 9.5$ Hz, $H_{4'}$), 5.01 (1H, dd, $^3J_{2'-3'} = 9.5$ Hz, $^3J_{2'-1'} = 8.0$ Hz, $H_{2'}$), 4.92 (1H, d, $^3J_{1'-2'} = 8.0$ Hz, $H_{1'}$), 4.51 (1H, ddd, $^2J_{7a-7b} = 11.0$ Hz, $^3J_{7a-6b} = 4.0$ Hz, $^3J_{7a-6a} = 2.5$ Hz, H_{7a}), 4.24 (1H, td, $^2J_{7a-7b} = {}^3J_{7b-6a} = 11.0$ Hz, $^3J_{7b-6b} = 2.5$ Hz, H_{7b}), 4.23 (1H, dd, $^2J_{6'a-6'b} = 12.0$ Hz, $^3J_{6'a-5'} = 2.0$ Hz, $H_{6'a}$), 4.07 (1H, dd, $^2J_{6'b-6'a} = 12.0$ Hz, $^3J_{6'b-5'} = 5.5$ Hz, $H_{6'b}$), 3.80 (1H, ddd, $^3J_{5'-4'} = 9.5$ Hz, $^3J_{5'-6'b} = 5.5$ Hz, $^3J_{5'-6a'} = 2.0$ Hz, $H_{5'}$), 2.96−2.83 (1H, m, H_5), 2.77 (1H, br dd, $^2J_{10a-10b} = 4.5$ Hz, $^3J_{10a-8} = 4.0$ Hz, H_{10a}), 2.73 (1H, ddd, $^3J_{8-9} = 8.5$ Hz, $^3J_{8-10a} = 4.0$ Hz, $^3J_{8-10b} = 2.5$ Hz, H_8), 2.58 (1H, dd, $^2J_{10b-10a} = 4.5$ Hz, $^3J_{10b-8} = 2.5$ Hz, H_{10b}), 2.15−1.90 (2H, m, H_6), 1.64 (1H, ddd, $^3J_{9-8} = 8.5$ Hz, $^3J_{9-5} = 5.0$ Hz, $^3J_{9-1} = 1.5$ Hz, H_9), 1.22, 1.15, 1.10, 1.09 (36H, 4s, $COC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 177.4, 177.0, 176.5 (4C, $COC(CH_3)_3$), 164.6 (C11), 151.5 (C3), 105.3 (C4), 95.6 (C1′), 93.6 (C1), 72.6 (C5′), 71.8 (C3′), 70.6 (C2′), 68.5 (C7), 67.8 (C4′), 61.6 (C6′), 48.0 (C8), 44.3 (C10), 40.1 (C9), 38.9, 38.8 (4C, $C(CH_3)_3$), 27.8(C5), 27.0, 26.9 (4C, $C(CH_3)_3$), 24.8 (C6); IR (ATR): ν 2973, 1737 (C═O), 1625, 1480, 1398, 1368, 1271, 1131, 1068, 985, 838, 761 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (4.14), 240 (4.32); MS (ESI$^+$): m/z 733 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{54}NaO_{14}$ [M + Na]$^+$, calcd 733.3400, found 733.3402.

Mixture of (8*R*,10)-Dihydroxy-2′,3′,4′,6′-*O*-tetrapivaloylsweroside (33a) and (8*S*,10)-Dihydroxy-2′,3′,4′,6′-*O*-tetrapivaloylsweroside (33b). To a solution of perpivaloylsweroside (**31**) (1.389 g, 2.0 mmol, 1 equiv) in THF/H_2O (42 mL/14 mL) were added NMO (407 mg, 3.0 mmol, 1.5 equiv) and a 2.5% solution of OsO_4 in *tert*-butyl alcohol (1.25 mL, 0.1 mmol, 0.05 equiv). The reaction was agitated at room temperature for 96 h and quenched by addition of 10 mL of a solution of $NaHSO_3$ (1 g/L). The mixture was filtered through Celite. THF was evaporated, and the residual aqueous phase was extracted by CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with 5% HCl aqueous solution (2 × 50 mL), 5% $NaHCO_3$ aqueous solution (2 × 50 mL), and brine (2 × 50 mL), dried ($MgSO_4$), and evaporated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98/2) to give a mixture (4/3) of inseparable compounds (**33a** and **33b**) as a white solid (1.053 g, 73%). The absolute configurations of the two diastereoisomers were determined by comparison with the literature.[59,68] ^{1}H NMR (300 MHz, $CDCl_3$, **33a** = A, **33b** = B): δ 7.59 (1H, d, $^4J_{3A-5A} = 2.5$ Hz, H_{3A}), 7.50 (1H, d, $^4J_{3B-5B} = 2.5$ Hz, H_{3B}) 5.84 (1H, d, $^3J_{1A-9A} = 1.5$ Hz, H_{1A}), 5.55 (1H, d, $^3J_{1B-9B} = 1.0$ Hz, H_{1B}), 5.32 (2H, t, $^3J_{3'-2'} = {}^3J_{3'-4'} = 9.5$ Hz, $H_{3'A}$, $H_{3'B}$), 5.01 (2H, t, $^3J_{4'-3'} = {}^3J_{4'-5'} = 9.5$ Hz, $H_{4'A}$, $H_{4'B}$), 5.03−4.94 (2H, m, $H_{2'A}$, $H_{2'B}$), 4.91 (1H, d, $^3J_{1'A-2'A} = 8.0$ Hz, $H_{1'A}$), 4.87 (1H, d, $^3J_{1'B-2'B} = 8.0$ Hz, $H_{1'B}$), 4.49−4.38 (2H, m, H_{7aA}, H_{7aB}), 4.28 (1H, dd, $^3J_{6'aB-6'bB} = 12.5$ Hz, $^3J_{6'aB-5'B} = 2.0$ Hz, $H_{6'aB}$), 4.21 (1H, dd, $^3J_{6'aA-6'bA} = 12.5$ Hz, $^3J_{6'aA-5'A} = 2.0$ Hz, $H_{6'aA}$), 4.20−4.10 (2H, m, H_{7bB}, H_{7bA}), 4.06 (1H, dd, $^2J_{6'bA-6'aA} = 12.5$ Hz, $^3J_{6'bA-5'A} = 5.5$ Hz, $H_{6'bA}$), 4.00 (1H, dd, $^2J_{6'bB-6'aB} = 12.5$ Hz, $^3J_{6'bB-5'B} = 5.5$ Hz, $H_{6'bB}$), 3.82−3.73 (2H, m, $H_{5'B}$, $H_{5'A}$), 3.69−3.41 (6H, m, H_{10B}, H_{10A}, H_{8B}, H_{8A}), 3.01−2.71 (2H, m, H_{5B}, H_{5A}), 2.70 (4H, br s, 4 OH), 2.20−2.13 (1H, m, H_{9A}), 2.11−1.68 (5H, m, H_{6A}, H_{6B}, H_{9B}), 1.20, 1.13, 1.08, 1.05 (72H, 4s, $COC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 178.2, 177.0, 176.7, 176.6, 176.4 (8C, $COC(CH_3)_3$), 165.3 (2C, $C11_B$, $C11_A$), 153.5 ($C3_A$), 152.0 ($C3_B$), 106.0 ($C4_A$), 104.7 ($C4_B$), 96.0 ($C1'_A$), 95.6 ($C1'_B$), 93.6 ($C1_A$), 92.9 ($C1_B$), 72.5 ($C5'_B$), 72.4 ($C5'_A$), 71.9 (2C, $C3'_B$, $C3'_A$), 70.7 (2C, $C2'_B$,$C2'_A$), 68.8 (2C $C8_B$, $C8_A$), 68.3 ($C7_A$), 68.2 ($C7_B$), 67.7 (2C, $C4'_B$, $C4'_A$), 66.3 ($C10_A$), 63.8 ($C10_B$), 61.5 ($C6'_A$), 61.4 ($C6'_B$), 39.9 ($C9_B$), 38.8, 38.7, 38.6 (8C, $C(CH_3)_3$), 37.7 ($C9_A$), 27.8 ($C5_B$), 27.3 ($C5_A$), 27.0, 26.9 (8C, $C(CH_3)_3$), 25.3 ($C6_B$), 24.8 ($C6_A$); IR (ATR): ν 2971, 1727 (C═O), 1617, 1480, 1398, 1278, 1140, 1068, 1024, 938, 840, 762 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (4.01), 239 (4.01); MS (ESI$^+$): m/z 751 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{56}NaO_{15}$ [M + Na]$^+$, calcd 751.3510, found 751.3510.

9-((8*R*)-12,12-Dimethyl-8,10-dioxolanyl)perpivaloylsweroside (34a) and 9-((8*S*)-12,12-Dimethyl-8,10-dioxolanyl)-perpivaloylsweroside (34b). To a solution of **33** (1.07 g, 1.48 mmol, 1 equiv) in acetone (20 mL) was added camphorsulfonic acid (CSA) (68.8 mg, 0.296 mmol, 0.2 equiv), and the mixture was agitated at room temperature for 24 h. Then silica was added, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (cyclohexane/AcOEt, 70/30) to give, in order of elution, the minor compound (*S*)-**34b** as a white solid (386.3 mg, 34%) and compound (*R*)-**34a** as a white solid (717.5 mg, 63%).

Major Compound: 9-((8R)-12,12-Dimethyl-8,10-dioxolanyl)-perpivaloylsweroside (34a). $[\alpha]_D = -111.5$ ($c = 0.23$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, d, $^4J_{3-5} = 2.5$ Hz, H_3), 5.82

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(1H, d, $^3J_{1-9}$ = 1.5 Hz, H_1), 5.32 (1H, t, $^3J_{3'-2'}$ = $^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.06 (1H, t, $^3J_{4'-5'}$ = $^3J_{4'-3'}$ = 9.5 Hz, $H_{4'}$), 4.98 (1H, dd, $^3J_{2'-3'}$ = 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 4.89 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.41 (1H, dm, $^2J_{7a-7b}$ = 11.0 Hz, H_{7a}), 4.21 (1H, dd, $^3J_{6'a-6'b}$ = 12.5 Hz, $^3J_{6'a-5'}$ = 2.0 Hz, $H_{6'a}$), 4.19−4.11 (1H, m, H_{7b}), 4.08 (1H, dd, $^2J_{10a-10b}$ = 7.5 Hz, $^3J_{10a-8}$ = 6.5 Hz, H_{10a}), 3.99 (1H, dd, $^2J_{6'b-6'a}$ = 12.5 Hz, $^3J_{6'b-5'}$ = 6.0 Hz, $H_{6'b}$), 3.85 (1H, dt, $^3J_{8-9}$ = 10.0 Hz, $^3J_{8-10a}$ = $^3J_{8-10b}$ = 6.5 Hz, H_8), 3.76 (1H, ddd, $^3J_{5'-4'}$ = 9.5 Hz, $^3J_{5'-6'b}$ = 6.0 Hz, $^3J_{5-6a'}$ = 2.0 Hz, $H_{5'}$), 3.56 (1H, dd, $^2J_{10b-10a}$ = 7.5 Hz, $^3J_{10b-8}$ = 6.5 Hz, H_{10b}), 2.97−2.85 (1H, m, H_5), 2.10 (1H, ddd, $^3J_{9-8}$ = 10.0 Hz, $^3J_{9-5}$ = 6.0 Hz, $^3J_{9-1}$ = 1.5 Hz, H_9), 1.75 (1H, dm, $^2J_{6a-6b}$ = 13.0 Hz, H_{6a}), 1.45 (1H, qd, $^3J_{6b-7b}$ = $^3J_{6b-5}$ = $^2J_{6b-6a}$ = 13.0 Hz, $^3J_{6b-7a}$ = 3.5 Hz, H_{6b}), 1.36, 1.28 (6H, 2s, CCH_3); 1.18, 1.12, 1.06, 1.05 (36H, 4s, COC(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 176.8, 176.6, 176.4 (4C, COC$(CH_3)_3$), 164.4 (C11), 152.9 (C3), 108.7 ($(CH_3)_2$C)) 104.3 (C4), 95.8 (C1′), 93.4 (C1), 72.4 (C5′), 71.8 (C8), 71.6 (C3′), 70.7 (C2′), 69.5 (C10), 67.9 (C7), 67.8 (C4′), 61.7 (C6′), 41.2 (C9), 38.7, 38.6, 38,5 (4C, C$(CH_3)_3$), 27.0, 26.9 (4C, C$(CH_3)_3$), 26.8 (C5), 26.4 (CH_3), 25.2 (C6), 24.9 (CH_3); IR (ATR): ν 2974, 1738 (C═O), 1625, 1480, 1398, 1270, 1132, 1066, 970, 893 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (4.21), 241 (4.13); MS (ESI$^+$): m/z 791 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{39}H_{60}NaO_{15}$ [M + Na]$^+$, calcd 791.3824, found 791.3823.

*Minor Compound: 9-((8S)-12,12-Dimethyl-8,10-dioxolanyl)-perpivaloylsweroside (**34b**).* $[\alpha]_D$ = −110.4 (c = 0.28, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (1H, d, $^4J_{3-5}$ = 2.5 Hz, H_3), 5.29 (1H, t, $^3J_{3'-2'}$ = $^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.40 (1H, d, $^3J_{1-9}$ = 1.0 Hz, H_1), 5.03 (1H, t, $^3J_{4'-5'}$ = $^3J_{4'-3'}$ = 9.5 Hz, $H_{4'}$), 4.96 (1H, br dd, $^3J_{2'-3'}$ = 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 4.85 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.41 (1H, dm, $^2J_{7a-7b}$ = 11.0 Hz, H_{7a}), 4.21 (1H, dd, $^2J_{6'a-6'b}$ = 12.0 Hz, $^3J_{6'a-5'}$ = 2.0 Hz, $H_{6'a}$), 4.12 (1H, tm, $^2J_{7b-7a}$ = $^3J_{7b-6b}$ = 12.0 Hz, H_{7b}), 3.96 (1H, dd, $^2J_{6'b-6'a}$ = 12.0 Hz, $^3J_{6'b-5'}$ = 6.0 Hz, $H_{6'b}$), 3.93 (1H, dd, $^2J_{10a-10b}$ = 8.0 Hz, $^3J_{10a-8}$ = 5.5 Hz, H_{10a}), 3.83 (1H, td, $^3J_{8-10b}$ = $^3J_{8-9}$ = 8.0 Hz, $^3J_{8-10a}$ = 5.5 Hz, H_8), 3.74 (1H, ddd, $^3J_{5'-4'}$ = 9.5 Hz, $^3J_{5'-6'b}$ = 6.0 Hz, $^3J_{5-6a'}$ = 2.0 Hz, $H_{5'}$), 3.58 (1H, t, $^2J_{10b-10a}$ = $^3J_{10b-8}$ = 8.0 Hz, H_{10b}), 2.89 (1H, dtd, $^3J_{5-6a}$ = 13.0 Hz, $^3J_{5-9}$ = $^3J_{5-6b}$ = 5.0 Hz, $^4J_{5-3}$ = 2.5 Hz, H_5), 2.14 (1H, ddd, $^3J_{9-8}$ = 8.0 Hz, $^3J_{9-5}$ = 5.0 Hz, $^3J_{9-1}$ = 1.0 Hz, H_9), 2.05 (1H, qd, $^3J_{6a-7a}$ = $^3J_{6a-5}$ = $^2J_{6a-6b}$ = 13.0 Hz, $^3J_{6a-7b}$ = 3.5 Hz, H_{6a}), 1.85 (1H, dm, $^2J_{6b-6a}$ = 13.0 Hz, H_{6b}), 1.31, 1.26 (6H, 2s, CCH_3), 1.17, 1.10, 1.04, 1.03 (36H, 4s, COC(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 176.8, 176.5, 176.4 (4C, COC$(CH_3)_3$), 164.6 (C11), 151.4 (C3), 109.1 ($(CH_3)_2$C), 105.9 (C4), 95.3 (C1′), 92.8 (C1), 72.5 (C5′), 71.8 (C8), 71.7 (C3′), 70.5 (C2′), 68.6 (C7), 67.8 (C4′), 67.2 (C10), 61.7 (C6′), 40.1 (C9), 38.7, 38.6, 38.5 (4C, C$(CH_3)_3$), 28.1 (C5), 27.0, 26.9, 26.7 (4C, C$(CH_3)_3$), 26.5, 26.0 (2C, CH_3), 25.4 (C6); IR (ATR): ν 2974, 1738 (C═O), 1625, 1480, 1398, 1270, 1132, 1066, 970, 893 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (4.21), 241 (4.13); MS (ESI$^+$): m/z 791 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{39}H_{60}NaO_{15}$ [M + Na]$^+$, calcd 791.3824, found 791.3823.

General Procedure GP02 for Lactone Ring-Opening of Secoiridoids Exemplified by the Synthesis of 11-Demethyl-(2,3′,4′,6′-*O*-tetrapivaloyl)secologanol (35). To a solution of **31** (50 mg, 0.072 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) was added a commercial solution of (TMS)ONa (1 M) in CH_2Cl_2 (140 μL, 0.14 mmol, 2 equiv). The reaction was stirred at room temperature for 2 h and quenched by addition of silica. After 15 min of stirring, the suspension was evaporated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 97/3) to give **35** as a white solid (45 mg, 88%). Note that **35** relactonizes to **31** in solution. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, s, H_3), 5.65 (1H, ddd, $^3J_{8-10a}$ = 17.5 Hz, $^3J_{8-10b}$ = 10.5 Hz, $^3J_{8-9}$ = 7.5 Hz, H_8), 5.36 (1H, d, $^3J_{1-9}$ = 8.0 Hz, H_1), 5.33 (1H, t, $^3J_{3'-2'}$ = $^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.28−5.19 (2H, m, $^3J_{10a-8}$ = 17.5 Hz, $^3J_{10b-8}$ = 10.5 Hz, H_{10}), 5.13 (1H, t, $^3J_{4'-3'}$ = $^3J_{4'-5'}$ = 9.5 Hz, $H_{4'}$), 5.04 (1H, dd, $^3J_{2'-3'}$ = 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 4.96 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.24 (1H, dd, $^2J_{6'a-6'b}$ = 12.0 Hz, $^3J_{6'a-5'}$ = 2.0 Hz, $H_{6'a}$), 4.05 (1H, dd, $^2J_{6'b-6'a}$ = 12.0 Hz, $^3J_{6'b-5'}$ = 5.5 Hz, $H_{6'b}$), 3.76 (1H, ddd, $^3J_{5'-4'}$ = 9.5 Hz, $^3J_{5'-6'b}$ = 5.5 Hz, $^3J_{5'-6a'}$ = 2.0 Hz, $H_{5'}$), 3.66−3.50 (2H, m, H_7), 2.82 (1H, dt, $^3J_{5-9}$ = 9.0 Hz, $^3J_{5-6a}$ = $^3J_{5-6b}$ = 5.0 Hz, H_5), 2.50 (1H, br td, $^3J_{9-5}$ = $^3J_{9-1}$ = 8.0 Hz, $^3J_{9-8}$ = 5.0 Hz, H_9), 1.97−1.84 (1H, m, H_{6a}), 1.50−1.40 (1H, m, H_{6b}), 1.19, 1.13, 1.09, 1.08 (36H, 4s, COC(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 177.1, 176.5, 176.4 (4C, COC$(CH_3)_3$), 172.5 (C11), 154.7 (C3), 133.1 (C8), 119.2 (C10), 109.5 (C4), 96.9 (C1′), 96.5 (C1), 72.4 (C5′), 72.0 (C3′), 70.6 (C2′), 67.7 (C4′), 61.6 (C6′), 59.7 (C7), 43.6 (C9), 38.8, 38.7, 38.6 (4C, C$(CH_3)_3$), 33.2 (C6), 29.6 (C5), 27.1, 27.0, 26.9 (4C, C$(CH_3)_3$); IR (ATR): ν 2917, 2874, 1740, 1680, 1631, 1480, 1460, 1398, 1278, 1133, 1067, 1035, 915, 733 cm^{-1}; MS (ESI$^+$): m/z 735 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{56}NaO_{14}$ [M + Na]$^+$, calcd 735.3568, found 735.3560.

7-Deoxy-10-hydroxy-11-demethyl-(2′,3′,4′,6′-*O*-tetrapivaloyl)morroniside (38) and 9-((8*S*)-Epoxy)-11-demethyl-(2′,3′,4′,6′-*O*-tetrapivaloyl)secologanol (36a). The title compounds were synthesized using general procedure GP02 with **32a** (35 mg, 0.05 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (100 μL, 0.1 mmol, 2 equiv) for 24 h. The general procedure afforded after purification by flash chromatography, in order of elution, compound **38** as a white solid (12.0 mg, 32%) and compound **36a** as a white solid (19.6 mg, 54%).

*9-((8S)-Epoxy)-11-demethyl-(2′,3′,4′,6′-O-tetrapivaloyl)-secologanol (**36a**).* Note that **36a** relactonizes to **32a** in solution. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (1H, br s, H_3), 5.50 (1H, d, $^3J_{1-9}$ = 7.0 Hz, H_1), 5.35 (1H, t, $^3J_{3'-2'}$ = $^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.14 (1H, t, $^3J_{4'-3'}$ = $^3J_{4'-5'}$ = 9.5 Hz, $H_{4'}$), 5.07 (1H, dd, $^3J_{2'-3'}$ = 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 4.99 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.23 (1H, dd, $^2J_{6'a-6'b}$ = 12.5 Hz, $^3J_{6'a-5'}$ = 2.0 Hz, $H_{6'a}$), 4.07 (1H, dd, $^2J_{6'b-6'a}$ = 12.5 Hz, $^3J_{6'b-5'}$ = 5.5 Hz, $H_{6'b}$), 3.78 (1H, ddd, $^3J_{5'-4'}$ = 9.5 Hz, $^3J_{5'-6'b}$ = 5.5 Hz, $^3J_{5'-6'a}$ = 2.0 Hz, $H_{5'}$), 3.71−3.63 (1H, m, H_{7a}), 3.62−3.54 (1H, m, H_{7b}), 3.35 (1H, br s, OH), 2.96−2.88 (2H, m, H_5, H_8), 2.81 (1H, dd, $^2J_{10a-10b}$ = 4.5 Hz, $^3J_{10a-8}$ = 3.0 Hz, H_{10a}), 2.75 (1H, t, $^2J_{10b-10a}$ = $^3J_{10b-8}$ = 4.5 Hz, H_{10b}), 2.07−1.95 (1H, m, H_{6a}), 1.88−1.80 (1H, m, H_9), 1.75−1.63 (1H, m, H_{6b}), 1.22, 1.15, 1.11, 1.10 (36H, 4s, COC-(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 177.1, 176.4 (4C, COC$(CH_3)_3$), 171.8 (C11), 154.8 (C3), 109.2 (C4), 96.9 (C1′), 95.3 (C1), 72.5 (C5′), 71.8 (C3′), 70.7 (C2′), 67.7 (C4′), 61.5 (C6′), 59.9 (C7), 50.6 (C8), 45.2 (C10), 41.4 (C9), 38.8, 38.7, 38.6 (4C, C$(CH_3)_3$), 33.2 (C6), 28.5 (C5), 27.1, 27.0, 26.9 (4C, C$(CH_3)_3$); IR (ATR): ν 2972, 1741, 1626, 1480, 1267, 1133, 1068, 940, 733 cm^{-1}; MS (ESI$^+$): m/z 751 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{56}NaO_{15}$ [M + Na]$^+$, calcd 751.3511, found 751.3507.

*9-((8R)-Epoxy)-11-demethyl-(2′,3′,4′,6′-O-tetrapivaloyl)-secologanol (**36b**).* The title compound was synthesized using general procedure GP02 with **32b** (35.5 mg, 0.05 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (100 μL, 0.1 mmol, 2 equiv) for 48 h. The general procedure afforded compound **36b** as a white solid (31.7 mg, 87%). $[\alpha]_D$ = −58.5 (c = 0.95, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, s, H_3), 5.43 (1H, d, $^3J_{1-9}$ = 9.0 Hz, H_1), 5.35 (1H, t, $^3J_{3'-2'}$ = $^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.13 (1H, t, $^3J_{4'-3'}$ = $^3J_{4'-5'}$ = 9.5 Hz, $H_{4'}$), 5.04 (1H, dd, $^3J_{2'-3'}$ = 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 4.96 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.24 (1H, dd, $^2J_{6'a-6'b}$ = 12.0 Hz, $^3J_{6'a-5'}$ = 2.0 Hz, $H_{6'a}$), 4.04 (1H, dd, $^2J_{6'b-6'a}$ = 12.0 Hz, $^3J_{6'b-5'}$ = 5.0 Hz, $H_{6'b}$), 3.77 (1H, ddd, $^3J_{5'-4'}$ = 9.5 Hz, $^3J_{5'-6'b}$ = 5.0 Hz, $^3J_{5'-6'a}$ = 2.0 Hz, $H_{5'}$), 3.70 (1H, dt, $^2J_{7a-7b}$ = 11.5 Hz, $^3J_{7a-6a}$ = $^3J_{7a-6b}$ = 5.5 Hz, H_{7a}), 3.63 (1H, ddd, $^2J_{7b-7a}$ = 11.5 Hz, $^3J_{7b-6a}$ = 9.0 Hz, $^3J_{7b-6b}$ = 4.0 Hz, H_{7b}), 3.02 (1H, dt, $^3J_{5-6b}$ = 9.0 Hz, $^3J_{5-9}$ = $^3J_{5-6a}$ = 5.0 Hz, H_5), 2.95−2.90 (1H, m, H_8), 2.91−2.87 (1H, m, H_{10a}), 2.59 (1H, dd, $^2J_{10b-10a}$ = 4.5 Hz, $^3J_{10b-8}$ = 2.0 Hz, H_{10b}), 2.13 (1H, dddd, $^2J_{6a-6b}$ = 14.0 Hz, $^3J_{6a-7b}$ = 9.0 Hz, $^3J_{6a-7a}$ = 5.5 Hz, $^3J_{6a-5}$ = 5.0 Hz H_{6a}), 1.54 (1H, dddd, $^2J_{6b-6a}$ = 14.0 Hz, $^3J_{6b-5}$ = 9.0 Hz, $^3J_{6b-7a}$ = 5.5 Hz, $^3J_{6b-7b}$ = 4.0 Hz, H_{6b}), 1.48 (1H, td, $^3J_{9-8}$ = $^3J_{9-1}$ = 9.0 Hz, $^3J_{9-5}$ = 5.0 Hz, H_9), 1.20, 1.14, 1.11, 1.10 (36H, 4s, COC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 177.1, 176.6, 176.4 (4C, COC$(CH_3)_3$); 172.2 (C11), 154.3 (C3), 109.3 (C4), 96.7 (C1′), 94.7 (C1), 72.6 (C5′), 71.7 (C3′), 70.5 (C2′), 67.6 (C4′), 61.5 (C6′), 59.7 (C7), 49.7 (C8), 48.6 (C10), 44.1 (C9), 38.8, 38.7, 38.8 (4C, C$(CH_3)_3$), 33.9 (C6), 27.8 (C5), 27.1, 27.0, 26.9 (4C, C$(CH_3)_3$); IR (ATR): ν 2971, 1741, 1629, 1481, 1277, 1134, 1067, 911, 732 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (3.66), 241 (3.99); MS (ESI$^+$): m/z 751 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{56}NaO_{15}$ [M + Na]$^+$, calcd 751.3511, found 751.3510.

*7-Deoxy-10-hydroxy-11-demethyl-(2′,3′,4′,6′-O-tetrapivaloyl)-morroniside (**38**).* $[\alpha]_D^{20}$ = −27.2 (c = 0.58, CH_2Cl_2); ^{1}H NMR (300

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MHz, $CDCl_3$): δ 7.50 (1H, br s, H_3), 5.42 (1H, t, $^3J_{3'-2'} = {}^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.26 (1H, d, $^3J_{1-9}$ = 9.5 Hz, H_1), 5.16 (1H, t, $^3J_{4'-3'} = {}^3J_{4'-5'}$ = 9.5 Hz, $H_{4'}$), 5.11 (1H, dd, $^3J_{2'-3'}$ = 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 5.03 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.27 (1H, dd, $^2J_{6'a-6'b}$ = 12.5 Hz, $^3J_{6'a-5'}$ = 1.5 Hz, $H_{6'a}$), 4.07 (1H, dd, $^2J_{6'b-6'a}$ = 12.5 Hz, $^3J_{6'b-5'}$ = 5.5 Hz, $H_{6'b}$), 3.97−3.86 (3H, m, H_{7a}, H_8, H_{10a}), 3.81 (1H, ddd, $^3J_{5'-4'}$ = 9.5 Hz, $^3J_{5'-6'b}$ = 5.5 Hz, $^3J_{5'-6'a}$ = 1.5 Hz, $H_{5'}$), 3.66 (1H, dd, $^2J_{10b-10a}$ = 12.5 Hz, $^3J_{10b-8}$ = 8.5 Hz, H_{10b}), 3.05 (1H, br t, $^2J_{7b-7a} = {}^3J_{7b-6b}$ = 12.5 Hz, H_{7b}), 3.04 (1H, dd, $^3J_{5-6b}$ = 10.0 Hz, $^3J_{5-9}$ = 6.0 Hz, H_5), 1.92 (1H, dt, $^3J_{9-1}$ = 9.5 Hz, $^3J_{9-5} = {}^3J_{9-8}$ = 6.0 Hz, H_9), 1.82 (1H, br d, $^2J_{6a-6b}$ = 14.5 Hz, H_{6a}), 1.51 (1H, dddd, $^2J_{6b-6a}$ = 14,5 Hz, $^3J_{6b-7b}$ = 12.5 Hz, $^3J_{6b-5}$ = 10.0 Hz, $^3J_{6b-7a}$ = 2.5 Hz, H_{6b}), 1.22, 1.16, 1.14, 1.11 (36H, 4s, $COC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 177.7, 177.0, 176.4 (4C, $COC(CH_3)_3$), 170.4 (C11), 152.8 (C3), 110.0 (C4), 96.2 (C1′), 96.0 (C1), 72.8 (C5′), 71.9 (C10), 71.7 (C7), 71.6 (C8), 71.2 (C3′), 70.7 (C2′), 67.7 (C4′), 61.5 (C6′), 47.0 (C9), 38.9, 38.8 (4C, $C(CH_3)_3$), 35.2 (C6), 32.8 (C5), 27.1, 27.0, 26.9 (4C, $C(CH_3)_3$); IR (ATR): ν 2971, 1739, 1633, 1480, 1277, 1132, 1068, 940, 737 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (3.58), 234 (3.70); MS (ESI$^+$): m/z 751 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{36}H_{56}NaO_{15}$ [M + Na]$^+$, calcd 751.3511, found 751.3507.

9-((8*S*)-12,12-Dimethyl-8,10-dioxolanyl)-11-demethyl-(2′,3′,4′,6′-*O*-tetrapivaloyl)secologanol (37b). The title compound was synthesized using general procedure GP02 with **34b** (76 mg, 0.1 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (200 μL, 0.2 mmol, 2 equiv) for 24 h. The general procedure afforded **37b** as a white solid (66 mg, 84%). $[\alpha]_D$ = −73.1 (c = 0.42, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, br s, H_3), 5.34 (1H, t, $^3J_{3'-2'} = {}^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.28 (1H, d, $^3J_{1-9}$ = 9.0 Hz, H_1), 5.13 (1H, t, $^3J_{4'-3'} = {}^3J_{4'-5'}$ = 9.5 Hz, $H_{4'}$), 5.00 (1H, dd, $^3J_{2'-3'}$= 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 4.92 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.25 (1H, dd, $^2J_{6'a-6'b}$ = 12.0 Hz, $^3J_{6'a-5'}$ = 2.0 Hz, $H_{6'a}$), 4.17 (1H, dd, $^2J_{10a-10b}$ = 8.5 Hz, $^3J_{10a-8}$ = 6.0 Hz, H_{10a}), 4.02 (1H, dd, $^2J_{6'b-6'a}$ = 12.0 Hz, $^3J_{6'b-5'}$ = 5.0 Hz, $H_{6'b}$), 4.10−3.92 (1H, m, H_8), 3.75 (1H, dd, $^3J_{5'-4'}$ = 9.5 Hz, $^3J_{5'-6'b}$ = 5.0 Hz, $^3J_{5'-6'a}$ = 2.0 Hz, $H_{5'}$), 3.71−3.55 (3H, m, H_7, H_{10b}), 2.85 (1H, m, H_5), 2.15−2.04 (1H, m, H_{6a}), 1.87 (1H, ddd, $^3J_{9-1} = {}^3J_{9-5}$ = 9.0 Hz, $^3J_{9-8}$ = 5.0 Hz, H_9), 1.35, 1.33 (6H, 2s, CH_3), 1.33−1.25 (1H, m, H_{6b}), 1.20, 1.14, 1.12, 1.10 (36H, 4s, $COC(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 177.1, 176.4, 176.3 (4C, $COC(CH_3)_3$), 172.5 (C11), 154.6 (C3), 109.9 (C4), 108.1 ($(CH_3)_2C$), 97.1 (C1′), 95.9 (C1), 73.0 (C8), 72.6 (C5′), 71.6 (C3′), 70.4 (C2′), 70.2 (C10), 67.5 (C4′), 61.4 (C6′), 59.9 (C7), 44.6 (C9), 38.8, 38.7, 38.6 (4C, $C(CH_3)_3$), 34.3 (C6), 27.8 (C5), 27.1, 27.0, 26.9 (4C, $C(CH_3)_3$), 26.5 (CH_3), 25.5 (CH_3); IR (ATR): ν 2973, 1741, 1633, 1480, 1277, 1132, 1060, 932, 761 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (3.98), 241 (4.06); MS (ESI$^+$): m/z 809 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{39}H_{62}NaO_{16}$ [M + Na]$^+$, calcd 809.3936, found 809.3953.

9-((8*R*)-12,12-Dimethyl-8,10-dioxolanyl)-11-demethyl-(2′,3′,4′,6′-*O*-tetrapivaloyl)secologanol (37a). The title compound was synthesized using general procedure GP02 with **34a** (76 mg, 0.1 mmol, 1 equiv) and (TMS)ONa (1 M) in CH_2Cl_2 (200 μL, 0.2 mmol, 2 equiv) for 39 h. The general procedure afforded **37a** as a white solid (51 mg, 65%). $[\alpha]_D$ = −110.4 (c = 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (1H, br s, H_3), 5.71 (1H, d, $^3J_{1-9}$ = 9.0 Hz, H_1), 5.35 (1H, t, $^3J_{3'-2'} = {}^3J_{3'-4'}$ = 9.5 Hz, $H_{3'}$), 5.14 (1H, t, $^3J_{4'-3'} = {}^3J_{4'-5'}$ = 9.5 Hz, $H_{4'}$), 5.08 (1H, br dd, $^3J_{2'-3'}$ = 9.5 Hz, $^3J_{2'-1'}$ = 8.0 Hz, $H_{2'}$), 5.03 (1H, d, $^3J_{1'-2'}$ = 8.0 Hz, $H_{1'}$), 4.22 (1H, br t, $^3J_{8-10}$ = 7.5 Hz, H_8), 4.17−4.10 (2H, m, $H_{6'}$), 3.96−3.88 (2H, m, H_{10}), 3.78 (1H, dm, $^3J_{5'-4'}$ = 9.5 Hz, $H_{5'}$), 3.64 (1H, br dt, $^2J_{7a-7b}$ = 11.0 Hz, $^3J_{7a-6a} = {}^3J_{7a-6b}$ = 4.0 Hz, H_{7a}), 3.50 (1H, br ddd, $^2J_{7b-7a}$ = 11.0 Hz, $^3J_{7b-6a}$ = 10.0 Hz, $^3J_{7b-6b}$ = 2.0 Hz, H_{7b}), 2.85 (1H, br ddd, $^3J_{5-6b}$ = 11.0 Hz, $^3J_{5-6a}$ = 5.0 Hz, $^3J_{5-9}$ = 4.0 Hz, H_5), 2.19 (1H, br dddd, $^2J_{6a-6b}$ = 14.0 Hz, $^3J_{6a-7b}$ = 10.0 Hz, $^3J_{6a-5}$ = 5.0 Hz, $^3J_{6a-7a}$ = 4.0 Hz, H_{6a}), 1.95 (1H, br dd, $^3J_{9-1}$ = 9.0 Hz, $^3J_{9-5}$ = 4.0 Hz, H_9), 1.32, 1.21 (6H, 2s, CH_3), 1.36−1.28 (1H, m, H_{6b}), 1.19, 1.13, 1.11, 1.09 (36H, 4s, $COC(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 177.1, 176.4, 176.3 (4C, $COC(CH_3)_3$), 172.8 (C11), 154.3 (C3), 109.6 (C4), 109.3 ($(CH_3)_2C$), 96.0 (C1′), 95.0 (C1), 75.5 (C8), 72.6 (C5′), 71.9 (C3′), 70.6 (C2′), 67.7 (C10), 67.6 (C4′), 61.7 (C6′), 59.5 (C7), 40.1 (C9), 39.8, 38.7 (4C, $C(CH_3)_3$), 34.1 (C6), 30.2 (C5), 27.1, 27.0 (4C, $C(CH_3)_3$), 26.3, 25.4 (2C, CH_3); IR (ATR): ν 2973, 1741, 1635, 1480, 1277, 1132, 1064, 892, 852, 736 cm^{-1}; UV (CH_2Cl_2): λ_{max} (log ε) 222 (3.98), 241 (4.06); MS (ESI$^+$): m/z 809 [M + Na]$^+$. HRMS (ESI$^+$): m/z for $C_{39}H_{62}NaO_{16}$ [M + Na]$^+$, calcd 809.3936, found 809.3953.

■ ASSOCIATED CONTENT

Supporting Information

Description of the experimental kinetic studies and ^{1}H and ^{13}C NMR spectra of the compounds. 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.

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