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Iodolactonization: Synthesis, Stereocontrol, and Compatibility Studies

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Generalized iodolactonization conditions have been developed for the formation of both *cis*- and *trans*-γ-lactones from 3-pentenoic acid derivatives containing various protected alcohol moieties. Kinetic control of the reaction using iodine and base at 0 °C for 6 h provided the *cis*-lactone with good selectivity (75:25), and thermodynamic control at room temperature for 24 h provided the *trans*-lactone with excellent selectivity (98:2).

Introduction

Iodolactonization of olefin-containing carboxylic acids and amides with high stereochemical fidelity continues to attract interest in organic synthesis, particularly in the total synthesis of bioactive compounds.[1] More specifically, γ-olefinic carboxylic acids and their derivatives can be transformed readily into primary iodo-γ-lactones.[2] γ-Lactone moieties exist in the structure of natural products, in both the *trans* and *cis* forms; thus, their diastereoselective syntheses are of general interest (see Figure 1 for examples).[3–6]

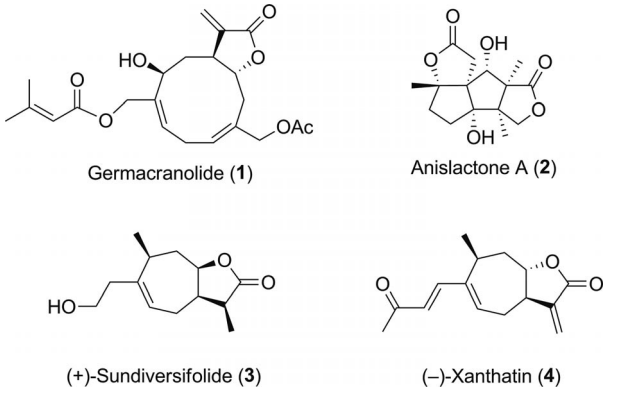
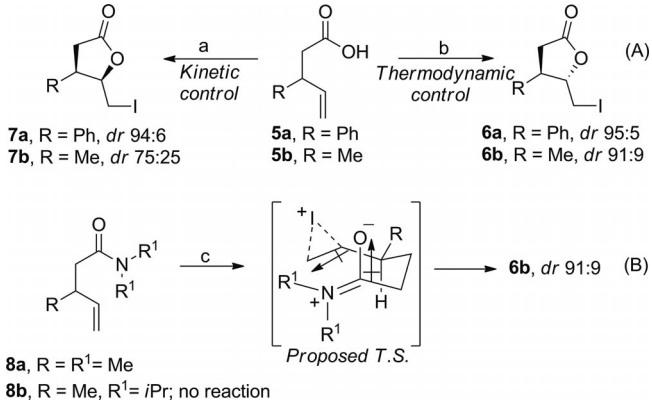


Figure 1. Representatives of natural products possessing *cis* and *trans*-γ-lactone cores.

As the iodolactonization of β-substituted γ-olefinic carboxylic acids can be thermodynamically or kinetically controlled to provide either the *trans*- or *cis*-iodo-γ-lactone with moderate to good selectivity, the iodolactonization of γ-olefinic esters and amides gives mainly the *trans*-iodo-γ-lactone with moderate selectivity.[1] Iodolactonization conditions cannot be generalized, because the diastereoselectivity and reactivity are sensitive to functional groups, steric hindrance, and electronic effects.[7,8] For instance, the diastereochemical outcome of the iodolactonization of γ-olefinic carboxylic acids **5a** and **5b**, having either a β-phenyl or β-methyl group, respectively, varies slightly under thermodynamic control but significantly under kinetic control [Scheme 1 (A)].[7]



Scheme 1. Thermodynamically and kinetically controlled iodolactonization of β-substituted γ-olefinic carboxylic acids and amides. Reagents and conditions:[7,8] (a) I_2, aqueous $NaHCO_3$, $CHCl_3$, 0 °C, 6 h; (b) I_2, MeCN, 0 °C to room temp., 24 h; (c) I_2, $MeCN/H_2O$, reflux, 24 h.

Similarly, the stereocontrol in the iodolactonization of γ-olefinic amides **8a** and **8b** is strongly affected by steric hindrance and electronic effects [Scheme 1 (B)].[8] The reaction proceeded with dimethylamide **8a**, whereas it failed to proceed with diisopropylamide **8b**. The diastereochemical outcome of the iodolactonization of **8a** was also solvent-dependent, rationalized as a consequence of the dipolar character of the transition states in the conformational equilibrium.[8] As iodolactonization conditions are either

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acidic or basic, the compatibility of any sensitive functional groups in the substrates must also be considered before choosing a method.

The lack of general methods for and functional-group sensitivity in iodolactonization reactions were of concern as we developed our synthetic strategy to approach the enantio- and diastereoselective total synthesis of *cis*,*cis*-germacranolide (**1**). This bioactive natural product, recently isolated from *Mikania thapsoides* DC.,[3] has yet to be synthesized chemically. Our retrosynthetic approach, illustrated in Figure 2, begins with an enantioselective conjugate addition to lactone **13**,[9] thus setting the absolute stereochemistry of the final target molecule. Diastereoselective iodolactonization[7,8] of addition product **12** will set the lactone stereocenters. Negishi cross-coupling[10] and Nozaki-Hiyama-Kishi (NHK) allylation[11] will provide the carbon atoms necessary to form the medium-sized ring by relay ring-closing metathesis (RRCM).[12] Since the total synthesis of this complex natural product requires protection of the reactive functional groups, the "R" group in **12** must be compatible with the iodolactonization reaction conditions. Herein, we describe a practical protocol for the preparation of γ-olefinic carboxylic acids, amides, and esters containing β-alcohol derivatives and the development of a general protocol for their use in diastereoselective iodolactonization reactions under thermodynamic and kinetic control to provide either *trans*- or *cis*-iodolactone derivatives, respectively.

Results and Discussion

The study began by evaluating the γ-olefinic amides dimethylamide **16** and pyrrolidine amide **19**, both with a *p*-methoxybenzyl (PMB) ether moiety, to see how the choice of amide would affect the selectivity in the iodolactonization reaction (Scheme 2). The synthesis of **16** began with vinyllactone **14**, which was obtained from **13** according to a literature procedure.[13] Compound **14** was converted to hydroxy dimethylamide **15** by treatment with $Me_2NH{\cdot}HCl$ and $AlMe_3$. The alcohol was then protected as PMB ether **16** in good yield by using standard conditions.[14] Similarly, treatment of **14** with pyrrolidine gave hydroxy pyrrolidine amide **18** quantitatively, and protection of the alcohol provided PMB ether **19**.

Iodolactonization of **16** and **19** under basic conditions [I_2 (4 equiv.), aqueous $NaHCO_3$, THF, –10 °C, 24 h] gave *trans*-iodo-γ-lactone **17a** in 40 and 45% yield, respectively. The product mixture also contained compounds without the PMB group, and some of the desired iodolactone underwent a reaction with the released amine. The *dr* values of crude **17a** resulting from **16** and **19** differed. PMB ether **16** gave **17a** with a *dr* of 64:36, and **19** gave **17a** with a *dr* of 75:25 (Table 1, Entries 1 and 2). Next, we replaced the PMB group with the bulkier protecting groups *tert*-butyldiphenylsilyl (TBDPS) and pivalate (Piv) to study their effect on the iodolactonization of the γ-olefinic pyrrolidine amide.

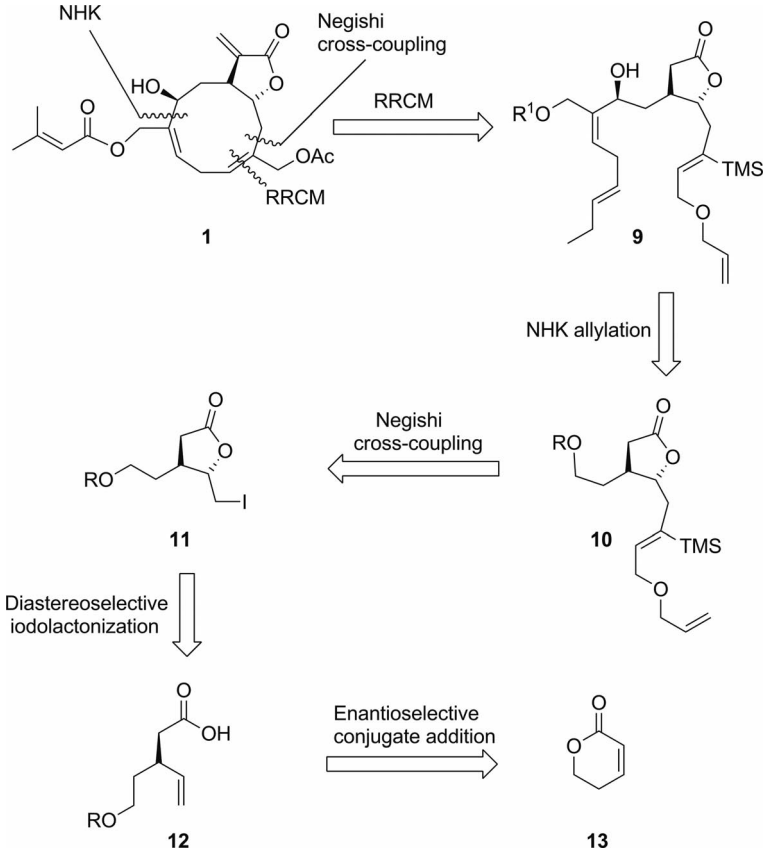
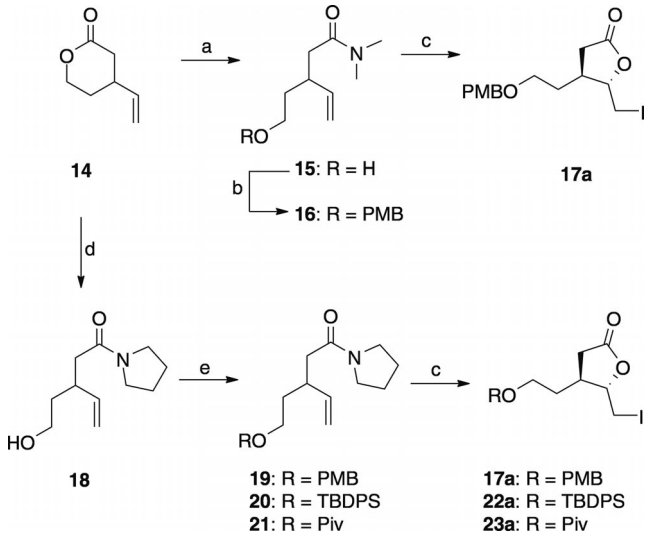


Figure 2. Retrosynthetic approach to *cis*,*cis*-germacranolide (**1**).



Scheme 2. Reagents and conditions: (a) $Me_2NH{\cdot}HCl$, $AlMe_3$, toluene, 60 °C, 16 h, 59%; (b) PMBCl, NaH, TBAI (tetra-*n*-butylammonium iodide), THF, room temp., 16 h, 85%; (c) I_2, THF, aqueous $NaHCO_3$, 24 h; (d) pyrrolidine, benzene, 60 °C, 16 h, 99%; (e) for **19**: PMBCl, NaH, TBAI, THF, room temp., 16 h, 85%; for **20**: TBDPSCl, imidazole, CH_2Cl_2, room temp., 16 h, 90%; for **21**: PivCl, DMAP, pyridine, THF, room temp., 16 h, 92%.

To this end, **18** was converted into silyl ether **20** and pivalate **21** in excellent yields (Scheme 2).[14] The iodolactonizations of **20** and **21** resulted in improved diastereoselectivity of the *trans*-iodo-γ-lactones **22a** and **23a** (*dr* for both was 80:20), but gave products in only moderate yields (Table 1, Entries 3 and 4). Unlike the benzyl moiety, both the TBDPS and Piv groups were stable under the reaction conditions. When the iodolactonization of **20** was carried out at 0 °C, the starting material was completely consumed within 5 h, but the yield and *dr* of **22a** decreased to 30% and 60:40, respectively (Table 1, Entry 5). No reaction occurred when the iodolactonization of **21** was carried out in THF/H_2O or $MeCN/H_2O$[8] at room temperature or heated at reflux, and the starting amide was recovered quantitatively (Table 1, Entry 6), which suggests that the reaction proceeds only under basic conditions.

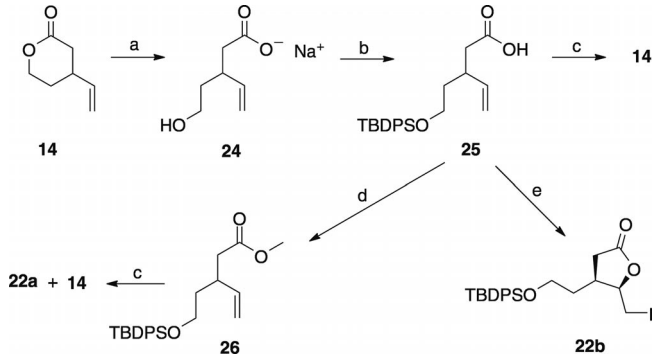
Table 1. Iodolactonization of γ-olefinic amides **16**, **19**, **20**, and **21**.

Entry	Substrate	γ-Lactone	Temp. [°C]	*dr*[c]	Yield [%][d]
1[a]	**16**	**17a**	–10	64:36	40
2[a]	**19**	**17a**	–10	75:25	45
3[a]	**20**	**22a**	–10	80:20	56
4[a]	**21**	**23a**	–10	80:20	52
5[a]	**20**	**22a**	0	60:40	30
6[b]	**21**	**23a**	23	–	–

[a] Reactions in Entries 1–5 were performed under condition (c) in Scheme 2. [b] Reactions were performed with I_2, THF/H_2O, –10 °C to room temp., 24 h. [c] Obtained by ^1H NMR spectroscopy. [d] Yield of isolated diastereomeric mixture after silica gel purification.

Although the separation of iodolactone diastereomers is generally difficult,[1–8] the ability to separate them by column chromatography on silica gel depended on the type of protecting group on the alcohol. More specifically, the iodolactone diastereomers with a TBDPS ether moiety were easily separated, whereas those with the other protecting groups were not.

With the results of the iodolactonization of γ-olefinic amides in hand, we turned our attention to the iodolactonization of γ-olefinic carboxylic acids and esters. The hydrolysis of amide **20** to its corresponding carboxylic acid under various conditions resulted in the deprotection and loss of the silyl group. The reduction of **20** with both DIBALH and LAH gave a mixture of products; however, treatment of **20** with Schwartz's reagent [$Cp_2Zr(H)Cl$] gave the aldehyde cleanly, but in only 30% yield.[15] As a result, the γ-olefinic carboxylic acids were synthesized instead from **14** (Scheme 3). Although the hydrolysis of **14** with NaOH followed by acidification resulted in rapid relactonization, the alcohol of sodium carboxylate **24** was readily protected as the TBDPS ether to give γ-olefinic carboxylic acid **25** in good recovery from **14**.



Scheme 3. Reagents and conditions: (a) NaOH, MeOH, 80 °C, 5 h; (b) TBDPSCl, imidazole, CH_2Cl_2, room temp., 16 h, 70%; (c) I_2, MeCN, 0 °C to room temp., 24 h; (d) $(CH_3)_3O^+BF_4^-$, iPr_2NEt, CH_2Cl_2, room temp., 24 h, 94%; (e) I_2, $CHCl_3$, H_2O, $NaHCO_3$, 6 h, 72%.

Attempts at the iodolactonization of **25** under thermodynamic conditions led to the regeneration of **14** as the only product. For a complete study, we converted **25** into γ-olefinic ester **26** by an esterification with Meerwein's reagent [$(CH_3)_3O^+BF_4^-$] and then subjected **26** to the same thermodynamic iodolactonization conditions.[16] Here, *trans*-iodo-γ-lactone **22a**, vinyllactone **14**, and the desilylated *trans*-iodo-γ-lactone were obtained, and hence desilylation was competitive with the iodolactonization. Similiar results were obtained when a TBS (*tert*-butyldimethylsilyl) protecting group was used in place of the TBDPS group.

We attributed the desilylation to the presence of I^-/HI in the solution and then rationalized that the presence of a base should prevent the desilylation by neutralizing the HI generated in situ. Hence, the iodolactonization of **25** was carried out with I_2 and anhydrous K_2CO_3 in MeCN at

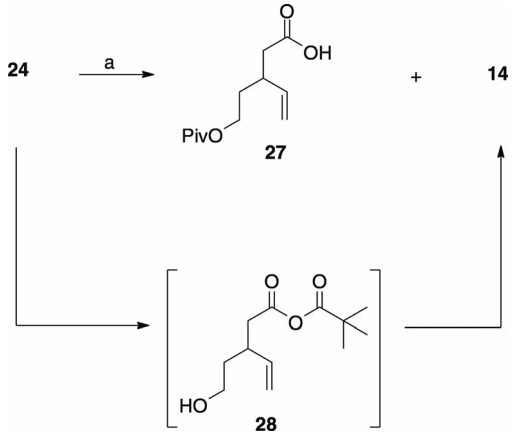
room temperature for 24 h to give the *cis*-iodo-γ-lactone **22b** with a *dr* of 56:44 (Table 2, Entry 2). The same result was obtained when the reaction was carried out with KI/I_2 and $NaHCO_3$ in THF/H_2O at room temperature for 24 h.[17] To improve the *dr* of **22b**, we carried out the iodolactonization of **25** under kinetic control. The expected *cis*-iodo-γ-lactone **22b** was obtained quantitatively with a maximiun *dr* of 75:25 (Table 2, Entry 3). The major *cis* isomer was quantitatively separated from the minor *trans* isomer, and both were fully characterized by NMR spectroscopy. This three-step diastereoselective synthesis of *cis*-iodo-γ-lactone **22b** from commercially available lactone **13** will serve as a powerful approach for the total synthesis of bioactive natural products such as **2** and **3** (Figure 1).

Table 2. Iodolactonization of γ-olefinic carboxylic acid **25**.

Entry	Substrate	γ-Lactone	Temp. [°C]	*dr*[d]	Yield [%][e]
1[a]	**25**	**22a**	23	–	–
2[b]	**25**	**22b**	23	56:44	53
3[c]	**25**	**22b**	0	75:25	72

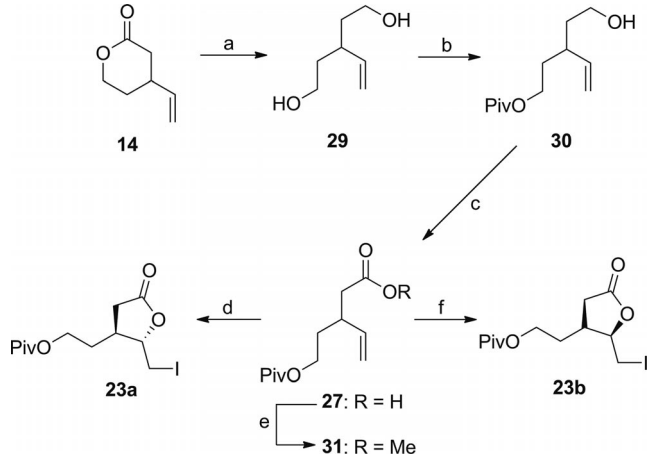
[a] Reaction was performed under condition (c) in Scheme 3. [b] Reaction was performed with I_2, MeCN, anhydrous K_2CO_3, room temp., 24 h. [c] Reaction was performed under condition (e) in Scheme 3. [d] Obtained by ^1H NMR spectroscopy. [e] Yield of isolated, pure *cis* isomer after silica gel purification.

We reasoned that by replacing the silyl group in **25** with a pivalate group, which is more stable under mildly acidic and basic conditions, we would enable the smooth iodolactonization of the γ-olefinic acid under thermodynamic control. Attempts to protect the alcohol of sodium carboxylate **24** as a pivalate under various conditions gave an inseparable mixture (50:50) of the desired γ-olefinic carboxylic acid **27** and **14** (Scheme 4). Lactonization of mixed anhydride **28**, generated in situ, would give rise to **14**.



Scheme 4. Reagents and conditions: (a) PivCl, DMAP, pyridine, THF, room temp., 16 h, 50:50 mixture of **27**/**14**.

However, reduction of **14** with LAH gave diol **29** in good yield (Scheme 5). Treatment of **29** with PivCl gave the monoprotected alcohol **30** in moderate yield, which then underwent PDC (pyridinium dichromate) oxidation to give the desired γ-olefinic carboxylic acid **27** in good yield.[18] Iodolactonization of **27** under thermodynamic control gave *trans*-iodo-γ-lactone **23a** in 98% yield with a *dr* of 98:2 (Table 3, Entry 1). Similarly, esterification of γ-olefinic carboxylic acid **27** to γ-olefinic ester **31** using Meerwein's reagent followed by iodolactonization under thermodynamic control gave **23a** in 89% yield with a *dr* of 98:2 (Table 3, Entry 2). γ-Olefinic acid **32** containing an acetyl group was prepared as illustrated in Scheme 6 with iodolactonization under thermodynamic control to give *trans*-iodo-γ-lactone **33a** in good yield with a *dr* of 97:3 (Table 3, Entry 3).



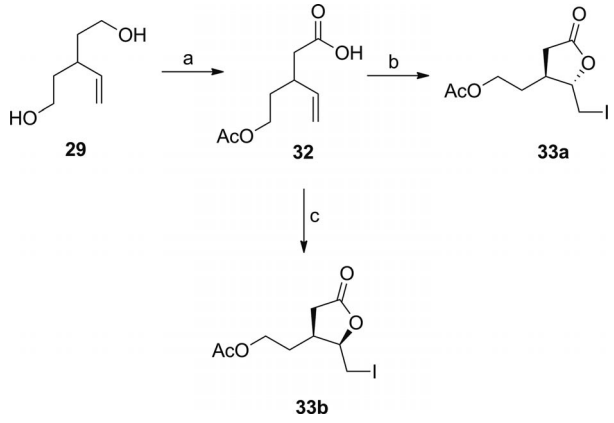
Scheme 5. Reagents and conditions: (a) LAH, Et_2O, THF, room temp., 12 h, 85%; (b) PivCl, DMAP, pyridine, room temp., 16 h, 65%; (c) PDC, DMF, 25 °C, 24 h, 84%; (d) I_2, MeCN, 0 °C to room temp., 24 h, 98–100%; (e) $(CH_3)_3O^+BF_4^-$, iPr_2NEt, CH_2Cl_2, room temp., 24 h, 93%; (f) I_2, $CHCl_3$, H_2O, $NaHCO_3$, 0 °C, 6 h, 93–100%.

Table 3. Thermodynamically and kinetically controlled iodolactonization of γ-olefinic carboxylic acids **27** and **32** and ester **31**.

Entry	Substrate	γ-Lactone	Temp. [°C]	*dr*[e]	Yield [%][f]
1[a]	**27**	**23a**	23	98:2	98
2[a]	**31**	**23a**	23	98:2	89
3[b]	**32**	**33a**	23	97:3	90
4[c]	**27**	**23b**	0	50:50	97
5[d]	**32**	**33b**	0	45:55	95

[a] Reactions were performed under condition (d) in Scheme 5. [b] Reaction was performed under condition (b) in Scheme 6. [c] Reaction was performed under condition (f) in Scheme 5. [d] Reaction was performed under condition (c) in Scheme 6. [e] Obtained by ^1H NMR spectroscopy. [f] Yield of isolated diastereomeric mixture after silica gel purification.

On the other hand, the kinetically controlled iodolactonization of γ-olefinic carboxylic acids **27** and **32** gave *cis*-iodo-γ-lactones **23b** and **33b** with disappointing diastereoselectivities (*dr* of 50:50 and 45:55, respectively; Table 3, Entries 4 and 5). Unlike **22**, the diastereomers of **23** and **33** were inseparable by column chromatography on silica gel.



Scheme 6. Reagents and conditions: (a) (i) AcCl, DMAP, pyridine, room temp., 16 h, 60%; (ii) PDC, DMF, 25 °C, 24 h, 84%; (b) I_2, MeCN, 0 °C to room temp., 24 h, 90–98%; (c) I_2, $CHCl_3$, H_2O, $NaHCO_3$, 0 °C, 6 h, 97%.

The stereochemistry of the γ-lactone ring was determined by using 2D NOESY NMR spectroscopic data for compounds **22a** and **22b** as shown in Figures 3 and 4, respectively. In Figure 3, the dipolar interaction between methine proton H_c in the lactone ring and the acyclic methylene protons H_a is much more intense than the interaction between the adjacent methine protons H_b and H_c in the lactone ring. This interaction supports the *trans* stereochemical assignment. In Figure 4, this relationship is reversed indicating that methine protons H_b and H_c have a *cis* stereochemistry.[19] In addition to the through-space evidence, other trends are observed with the chemical shifts and coupling constants between the methine protons. The shift for methine proton H_c is approximately 0.5 ppm larger in the *cis* than the *trans* lactone. Likewise, the methine proton H_b in the *cis* isomer is deshielded by approximately 0.3 ppm.[19] In addition to the shift values, the vicinal ^3J coupling between the methine protons is notably larger in the *cis* in comparison to the *trans* lactone rings. The chemical shift and *J* coupling trends are consistent with other lactone rings that we have synthesized and are listed in Table 4.

Table 4. Chemical shift and ^3J coupling values for the methine protons of the lactone ring.

Entry	γ-Lactone	*cis*/*trans*	H_c [ppm]	H_b [ppm]	$^3J_{\beta-\gamma}$ [Hz]
1	**17a**	*trans*	4.16	2.47	4.2
2	**22a**	*trans*	4.12	2.55	3.3
3	**23a**	*trans*	4.12	2.44	3.2
4	**22b**	*cis*	4.69	2.87	6.0
5	**23b**	*cis*	4.68	2.71	5.6
6	**23a**	*trans*	4.14	2.44	3.7

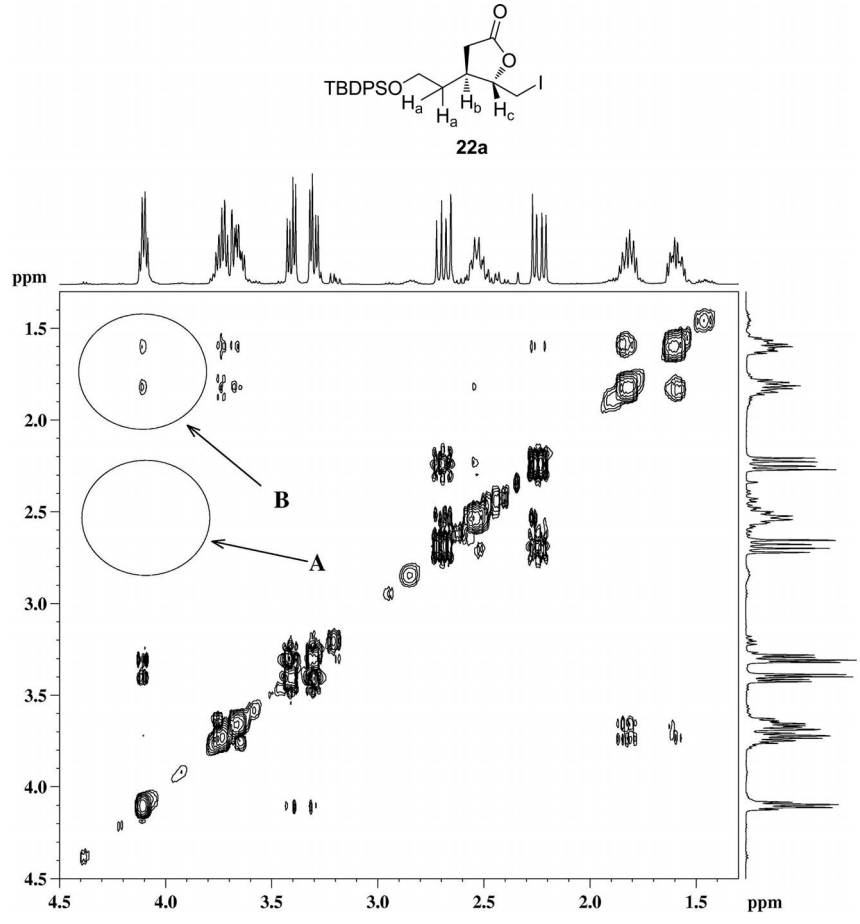


Figure 3. 400 MHz 2D NOESY spectrum of **22a**. Arrow A indicates the region void of dipolar interactions between methine protons H_b and H_c in the lactone ring. Arrow B indicates the dipolar interaction between γ-methine proton H_c and acyclic methylene protons H_a.

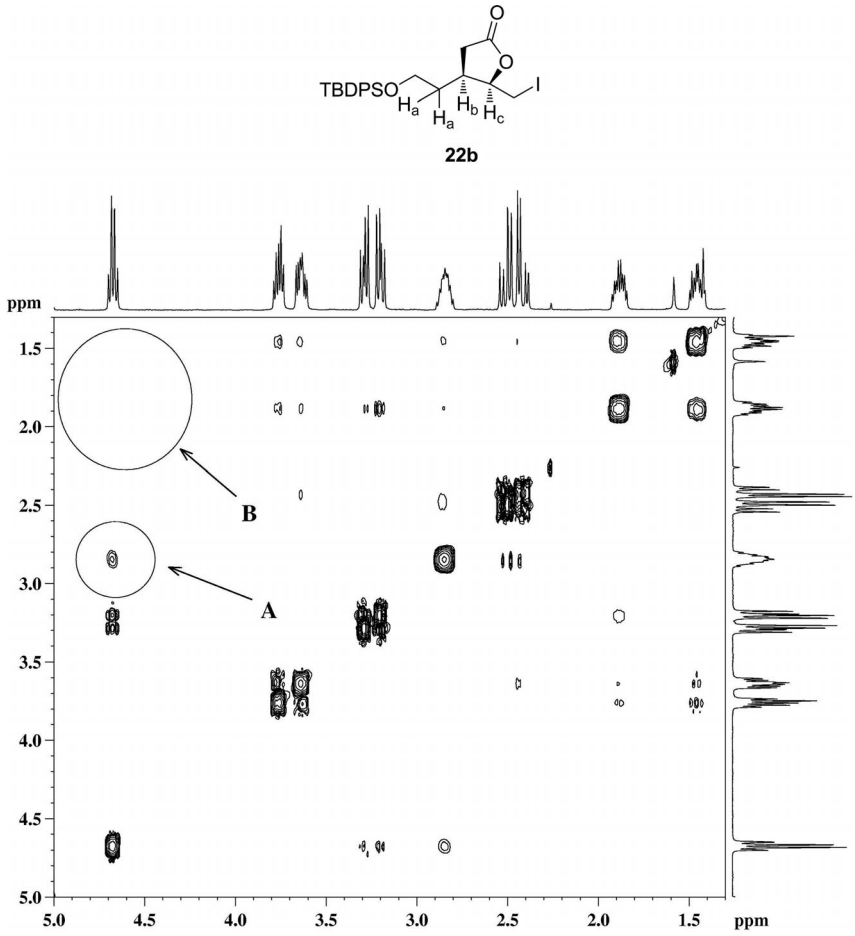


Figure 4. 400 MHz 2D NOESY spectrum of **22b**. Arrow A indicates the dipolar interaction between methine protons H_b and H_c in the lactone ring. Arrow B indicates the region void of dipolar interactions between γ-methine proton H_c and acyclic methylene protons H_a.

Conclusions

We have described a practical approach for the diastereoselective iodolactonization reaction under thermodynamic and kinetic control of γ-olefinic carboxylic acids, amides, and esters containing sensitive functional groups. Although the PMB ether was not particularly stable, using the TBDPS and pivalate groups instead provided stability, but gave low to moderate yields during the iodolactonization of γ-olefinic amides. The bulkiness of the *tert*-butyldiphenylsilyl ether and pivalate groups slightly improved the diastereoselectivity of the *trans*-iodo-γ-lactone product. In all cases, the iodolactonization of the γ-olefinic amides we studied resulted in low yields and moderate diastereoselectivity.

In the case of γ-olefinic carboxylic acids, cleavage of the TBDPS ether dominated under thermodynamically controlled iodolactonization; however, with a γ-olefinic ester, iodolactonaization was competitive with desilylation. Under kinetic control, desilylation was completely avoided, and decent selectivity for the *cis*-iodolactone resulted. Additionally, diastereomers of the iodolactones with a TBDPS ether moiety were easily separated by column chromatography on silica gel. Iodolactonization of γ-olefinic carboxylic acids containing acetate and pivalate groups gave excellent yields and diastereoselectivities under thermodynamic control, whereas excellent yields and poor diastereoselectivities were obtained under kinetic control.

We believe the results of this iodolactonization study offer a practical synthetic advantage in the synthesis of lactone-containing natural products. The use of *cis*-iodo-γ-lactone **22b** and *trans*-iodo-γ-lactone **23a** for the total synthesis of (+)-sundiversifolide (**3**) and *cis,cis*-germacranolide **1** are currently underway in our laboratories.

Experimental Section

General Methods: NMR spectra were recorded at room temperature with either a Bruker AV 400 with a 5 mm BBFO-Z-ATM probe or a Bruker DRX 600 with a 5 mm TXI (^1H, ^{13}C, ^{15}N) z-gradient probe. The chemical shifts for the ^1H NMR spectroscopic data are given in parts per million (ppm) and referenced to the residual $CHCl_3$ signal at δ = 7.26 ppm in deuterated chloroform. All NMR experiments were performed by using the standard Bruker pulse program library without further modification. For chemical shift and coupling determination, the 1D ^1H NMR spectra were acquired at 600 MHz with 8 scans with a spectral width of 8865 Hz and 32k data points. A 1D selective COSY experiment

with a 270° selective pulse of 75 ms was used to determine specific *J* coupling values shown in Table 4.[20] The ^{1}H spectra were processed by using a Gaussian broadening value of 0.5 and an exponential broadening value of –0.5 Hz. Compounds **22a** and **22b** were fully assigned by using 2D COSY, NOESY, HSQC (heteronuclear single quantum coherence), HMBC, and 1D ^{13}C experiments. The 2D NOESY experiments were acquired with 2048 × 256 data points by using 64 scans per increment and a mixing time of 600 ms. One zero fill was performed in both domains by using a shifted (sinebell)^2 window function.

Preparation of *trans*-5-(Iodomethyl)-4-{2-[(4-methoxybenzyl)oxy]-ethyl}dihydrofuran-2(3*H*)-one (17a)

From Dimethyl Amide 16: To a solution of dimethylamide **16** (58.10 mg, 0.19 mmol) in THF (1 mL) and saturated aqueous $NaHCO_3$ (0.50 mL) at –10 °C in a flask that was wrapped with aluminum foil was added I_2 (0.20 g, 0.79 mmol). The mixture was stirred in the dark at –10 °C for 24 h. Saturated aqueous $Na_2S_2O_3$ (1.60 mL) and Et_2O (2 mL) were added to quench the reaction. The aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (50% Et_2O in pentane and then 100% Et_2O; R_f = 0.13 in 100% Et_2O) to afford **17a** (30 mg, 40%, *dr* 80:20) as a yellow oil.

From Pyrrolidinyl Amide 19: To a solution of pyrrolidine amide **19** (60.31 mg, 0.19 mmol) in THF (1 mL) and saturated aqueous $NaHCO_3$ (0.50 mL) at –10 °C in a flask that was wrapped with aluminum foil was added I_2 (0.20 g, 0.79 mmol). The mixture was stirred in the dark at –10 °C for 24 h. Saturated aqueous $Na_2S_2O_3$ (1.60 mL) and Et_2O (2 mL) were added to quench the reaction. The aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (50% Et_2O in pentane and then 100% Et_2O; R_f = 0.13 in 100% Et_2O) to afford **17a** (33 mg, 45%, *dr* 80:20) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.14 (d, *J* = 7.2 Hz, 2 H), 6.89 (d, *J* = 7.2 Hz, 2 H), 4.43 (s, 2 H), 4.34–4.12 (m, 1 H), 3.82 (s, 3 H), 3.75–3.38 (m, 3 H), 3.38–3.26 (m, 1 H), 2.79 (dd, *J* = 17.8, 9.1 Hz, 1 H), 2.63–2.35 (m, 1 H), 2.35–2.26 (m, 1 H), 1.90 (dd, *J* = 13.8, 6.5 Hz, 1 H), 1.72 (dd, *J* = 13.7, 6.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 175.2, 159.2, 129.9, 129.8, 129.3, 129.2, 128.9, 113.8, 83.1, 72.7, 67.5, 67.3, 55.2, 38.8, 35.1, 33.2, 7.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{19}IO_4$ $[M + H]^+$ 391.0406; found 391.0408.

***trans*-4-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-5-(iodomethyl)dihydrofuran-2(3*H*)-one (22a):** To a solution of amide **20** (0.96 g, 2.20 mmol) in THF (12.80 mL) and saturated aqueous $NaHCO_3$ (6.80 mL) at –10 °C in a flask that was wrapped with aluminium foil was added I_2 (2.24 g, 8.80 mmol). The mixture was stirred in the dark at –10 °C for 23 h. Saturated aqueous $Na_2S_2O_3$ (25 mL) and Et_2O (25 mL) were added to quench the reaction. The colorless aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (40% Et_2O in pentane; R_f = 0.48) to afford **22a** (0.63 g, 56%, *dr* 80:20) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 6.7 Hz, 4 H), 7.45–7.36 (m, 6 H), 4.12 (dd, *J* = 10.4, 5.2 Hz, 1 H), 3.93–3.56 (m, 2 H), 3.42 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.32 (dd, *J* = 11.0, 4.6 Hz, 1 H), 2.70 (dd, *J* = 17.7, 9.1 Hz, 1 H), 2.53 (dd, *J* = 16.1, 9.9 Hz, 1 H), 2.25 (dd, *J* = 17.7, 7.7 Hz, 1 H), 1.84 (dt, *J* = 12.8, 5.3 Hz, 1 H), 1.61 (dt, *J* = 13.8, 6.7 Hz, 1 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 135.4, 133.1, 133.1, 129.8, 127.7, 82.9, 61.3, 38.3, 35.9, 34.8, 26.8, 19.0, 6.9 ppm. HRMS (ESI): calcd. for $C_{23}H_{29}IO_3Si$ $[M + H]^+$ 509.1009; found 509.1009.

Preparation of *trans*-2-[2-(Iodomethyl)-5-oxotetrahydrofuran-3-yl]-ethyl Pivalate (23a)

From Ester 31: To a stirred solution of ester **31** (6.18 g, 25.48 mmol) in MeCN (100 mL) at 0 °C in a flask that was wrapped with aluminium foil was added I_2 (19.50 g, 76.45 mmol). The reaction mixture was warmed to room temp. and stirred for 24 h. The reaction mixture was then quenched with an excess amount of a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and the mixture stirred until it was colorless. The mixture was then extracted with Et_2O (4 × 100 mL), and the combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (50% Et_2O in pentane; R_f = 0.30) afforded **23a** (8.05 g, 89%, *dr* 98:2) as a yellow oil.

From Acid 27: To a stirred solution of acid **27** (10.00 g, 43.81 mmol) in MeCN (500 mL) at 0 °C in a flask that was wrapped with aluminium foil was added I_2 (33.36 g, 131.42 mmol). The reaction mixture was warmed to room temp. and stirred for 24 h. The reaction mixture was quenched with an excess amount of a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and stirred until it was colorless. The mixture was then extracted with Et_2O (4 × 120 mL), and the combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (50% Et_2O in pentane; R_f = 0.30) afforded **23a** (15.52 g, 98%, *dr* 98:2) as a yellow oil. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 4.13 (dt, *J* = 10.5, 5.1 Hz, 3 H), 3.37 (ddd, *J* = 15.4, 11.0, 5.0 Hz, 2 H), 2.85 (dd, *J* = 17.6, 8.9 Hz, 1 H), 2.49–2.41 (m, 1 H), 2.40 (dd, *J* = 16.0, 7.2 Hz, 1 H), 1.99–1.93 (m, 1 H), 1.81–1.72 (m, 1 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 174.6, 82.5, 61.7, 38.6, 38.3, 34.7, 32.3, 27.1, 6.5 ppm. HRMS (ESI): calcd. for $C_{12}H_{19}IO_4$ $[M + H]^+$ 355.0406; found 355.0406. $C_{12}H_{19}IO_4$ (354.18): calcd. C 40.69, H 5.41; found C 40.33, H 5.47.

***cis*-4-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-5-(iodomethyl)dihydrofuran-2(3*H*)-one (22b):** A mixture of **25** (0.15 g, 0.39 mmol) and $NaHCO_3$ (99 mg, 1.18 mmol) in water (2.5 mL) was stirred at room temp. for 10 min before adding chloroform (2.5 mL). The mixture was cooled to 0 °C and stirred for 15 min before adding I_2 (200 mg, 0.78 mmol) in the dark. The mixture was stirred at 0 °C for 6 h, and then it was quenched with saturated aqueous NaS_2O_3 and the mixture agitated until the solution turned colorless or pale yellow. Et_2O (20 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (20 mL), and the combined organic layers were washed successively with water (10 mL) and then brine (10 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The diastereomeric mixture was separated by silica gel column chromatography (40% Et_2O in pentane; R_f = 0.53) to afford **22b** (0.63 g, 72%, single diastereomer) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.0 Hz, 4 H), 7.47–7.35 (m, 6 H), 4.67 (q, *J* = 6.6 Hz, 1 H), 3.75 (dt, *J* = 10.3, 5.0 Hz, 1 H), 3.68–3.54 (m, 1 H), 3.28 (dd, *J* = 10.5, 6.6 Hz, 1 H), 3.19 (dd, *J* = 10.4, 7.1 Hz, 1 H), 2.90–2.79 (m, 1 H), 2.45 (qd, *J* = 17.5, 7.2 Hz, 2 H), 1.93–1.82 (m, 1 H), 1.50–1.27 (m, 1 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 135.4, 133.1, 129.8, 127.7, 81.4, 77.3, 76.9, 76.6, 61.4, 35.5, 34.2, 29.5, 26.8, 19.1, 1.1 ppm. HRMS (ESI): calcd. for $C_{23}H_{29}IO_3Si$ $[M + H]^+$ 509.1009; found 509.1008. $C_{23}H_{29}IO_3Si$ (508.47): calcd. C 54.33, H 5.75; found C 54.34, H 5.74.

***trans*-2-[2-(Iodomethyl)-5-oxotetrahydrofuran-3-yl]ethyl Acetate (33a):** To a stirred solution of acid **32** (1.50 g, 8.06 mmol) in MeCN (100 mL) at 0 °C in the dark using a flask wrapped in aluminium foil was added I_2 (6.14 g, 24.19 mmol). The mixture was stirred at room temp. for 16 h. The reaction was quenched with an excess amount of saturated aqueous $Na_2S_2O_3$ and the mixture stirred until it turned colorless. This mixture was extracted with Et_2O (3×20 mL), and the combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (80% Et_2O in pentane; R_f = 0.37) afforded **33a** (2.26 g, 90%, *dr* 97:3) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31–4.08 (m, 3 H), 3.39 (ddd, J = 15.4, 11.0, 5.0 Hz, 2 H), 2.86 (dd, J = 17.7, 8.9 Hz, 1 H), 2.53–2.41 (m, 1 H), 2.35 (dd, J = 17.7, 7.4 Hz, 1 H), 2.08 (s, 3 H), 2.02–1.93 (m, 1 H), 1.83–1.74 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 170.7, 82.7, 61.8, 38.3, 34.8, 32.20, 20.8, 6.5 ppm. HRMS (ESI): calcd. for $C_9H_{13}IO_4$ $[M + H]^+$ 312.9937; found 312.9936. $C_9H_{13}IO_4$ (312.10): calcd. C 34.63, H 4.20; found C 35.00, H 4.42.

Supporting Information (see footnote on the first page of this article): Synthetic procedures and ^{1}H and ^{13}C NMR spectra.

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