Doubly Diastereoselective Iodolactonizations: Olefin and Face Selectivity in Nona-2,7-diene-5-carboxylic Acid Cyclizations

John C. McKew, Marilyn M. Olmstead, and Mark J. Kurth*,[1]

Department of Chemistry, University of California, Davis, California 95616

Received January 25, 1994•

Nonracemic nonadienoic acids (v) were subjected to iodolactonization conditions and, by doubly diastereoselective cyclization, delivered enantiomerically pure iodo lactones replete with up to five contiguous stereogenic centers.

The halolactonization reaction of β,γ- and γ,δ-unsaturated carboxylic acids has been used extensively by chemists for the better part of a century.[2] More recent applications of this reaction have been in the field of acyclic stereocontrol, and reaction conditions have been developed which deliver excellent 1,2- and 1,3-asymmetric induction under both thermodynamic[3] and kinetic[4] control. Coupling that versatility with synthetic strategies which selectively engage one of two diastereotopic functional groups would provide a unique exploitation of molecular symmetry.[5] In that context, we have reported a novel vicinal dialkyl-directed kinetic iodolactonization[6] which is unique in that it proceeds with double diastereoselectivity, delivering concomitant *olefin* and *face* selectivity. Thus, when racemic substrate **i** (Figure 1) was treated with iodine, iodolactonization ensued with exceptional 147:1 olefin selectivity and 30:1 face selectivity; of the four possible iodo lactone products, **ii** was obtained with 92% diastereoselectivity (ds). This remarkable result led us to extend our investigation of concomitant olefin- and face-selective transformations to the chiral auxiliary-mediated iodolactonization of amide **iii**[7] and the 1,3-dipolar cycloaddition of nitrile oxide **iv**.[8]

While electrophilic cyclization of amide **iii** provides enantioselective access to iodo lactones, amide derivatives of **i** with Cβ and C'β stereogenic centers are not accessible by Cα-alkylation of chiral amides. Here we report details of a study wherein nonracemic dienoic acids (see **v** in Figure 2) were subjected to iodolactonization conditions and, by doubly diastereoselective cyclization, delivered enantiomerically pure iodo lactones replete with up to five contiguous stereogenic centers, *a transformation which proceeds with concomitant group and face selectivity.*

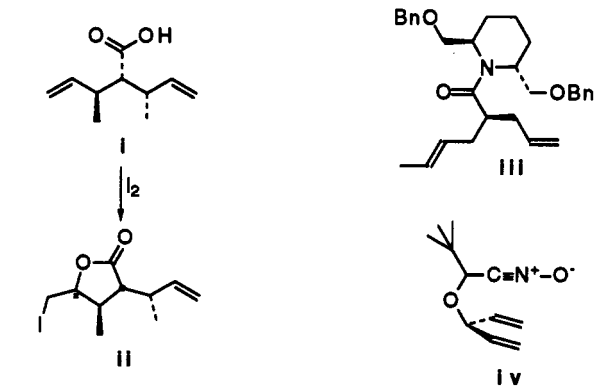


Figure 1.

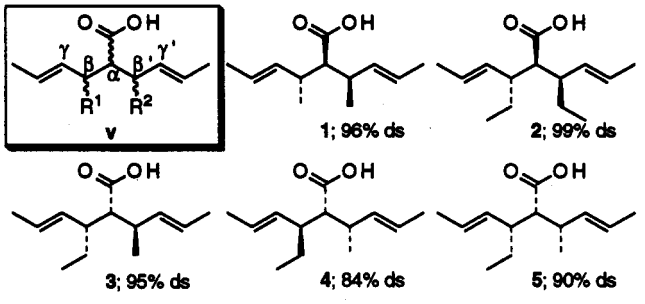


Figure 2.

However, vanguard to this objective is the need for ready enantioselective access to dienoic acids of general structure **v**. Indeed, versatility in the preparation of nonracemic iodo lactones requires both high double diastereoselectivity in the key electrophilic cyclization and a viable route to the starting dienoic acids which proceeds with excellent enantio- and diastereoselectivity as well as high pliancy in delivering any needed stereochemistry at the three contiguous stereogenic centers of **v**. We recently reported a synthesis of enantiomerically pure secondary allylic alcohols from ethyl lactate[9] and the subsequent use of these alcohols in an iterative[10] enolate Claisen rearrangement[11] to prepare dienoic acids of general structure **v**.[12] Specific to this report, dienoic acids **1-5** were prepared by this four-step method; each substrate was synthesized with

• Abstract published in *Advance ACS Abstracts*, May 1, 1994.

(1) M.J.K. is an NIH RCDA recipient (1989–1994; EC00182).

(2) For reviews of the halolactonization reaction, see: (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171–97. (b) Bartlett, Paul A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, 1983; Vol. 3, pp 411–54. (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–408.

(3) Bartlett, P. A.; Richardson, D. P; Myerson, J. *Tetrahedron* **1984**, *40*, 2317–27.

(4) (a) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.-I.; Yoshida, Z. I.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079–85. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819–25. (c) Günther, H. J.; Guntrum E.; Jäger, V. *Liebigs Ann. Chem.* **1984**, 15–30.

(5) Notable examples of this concept include Hoye's kinetic hydroxyazelaic acid lactonization[5a,b] and Schreiber's thermodynamic trihydroxynonanone spiroketalization.[5c] (a) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618–20. (b) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738–9. (c) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303–5.

(6) Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844–5.

(7) Najdi, S.; Reichlin, D.; Kurth, M. J. *J. Org. Chem.* **1990**, *55*, 6241–4.

(8) Kim, H. R.; Kim, H. J.; Duffy, J. L.; Olmstead, M. M.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* **1991**, *32*, 4259–62.

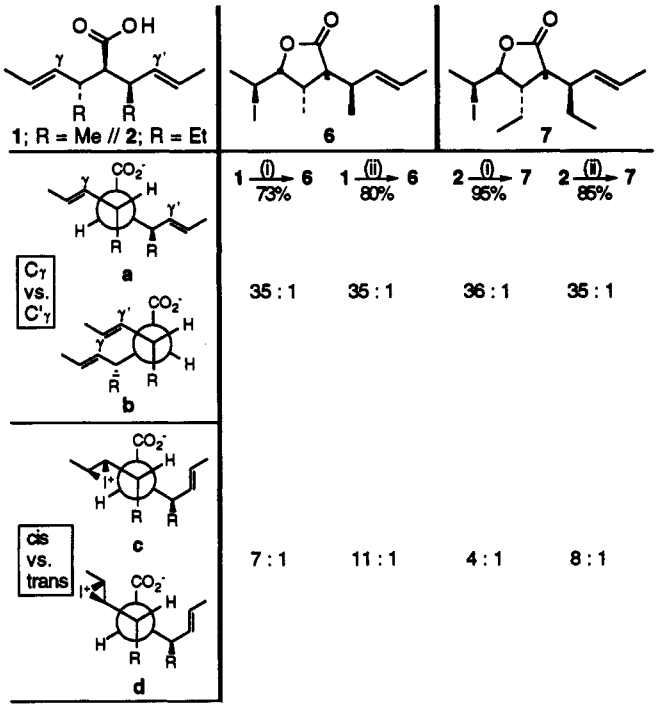
(9) McKew, J. C.; Kurth, M. J. *Org. Prep. Proced. Int.* **1993**, *25*, 125–30.

(10) For extensive reviews of tandem and iterative rearrangements, see: (a) Ziegler, F. E. Consecutive Rearrangements. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, Chapter 7.3. (b) Nakai, T.; Mikami, K. *Kagaku no Ryoiki* **1982**, *36*, 661–72; *Chem. Abstr.* **1983**, *98*, 16001K.

(11) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–77. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–52.

0022-3263/94/1959-3389$04.50/0

Table 1. Stereoselectivities in the Iodolactonization of Dienoic Acids 1 and 2[a]



[a] Key: (i) Saturated aqueous $NaHCO_3/CH_2Cl_2/I_2$, rt; (ii) THF/ ^nBuLi then I_2, −78 °C.

the indicated diastereoselectivity and with ≥98% enantiomeric excess.

In the iodolactonization of dienoic acids **1** and **2**, the nucleophilic carboxylate is confronted with flanking diastereotopic olefins which, as a consequence of resident stereochemistry, experience markedly different ground-state conformational positions relative to the carboxylate. This interplay between olefin reactivity and conformational bias (conformation **a** versus **b** as illustrated in Table 1) leads to high Cγ-selectivity (≥35:1::Cγ:C′γ) in these cyclization reactions.

Olefin face selectivity, which results in *cis*- versus *trans*-selectivity (C4–C5 relative stereochemistry) in iodo lactone products **6** and **7**, reflects the relative reactivity of iodonium intermediates **c** and **d**. Presumably, these iodonium ions are in rapid prior equilibrium with the starting dienoic acid, and not surprisingly, the resulting diastereoselectivity is subject to iodolactonization reaction conditions. Thus, while a room-temperature, two-phase carboxylate mixture (*i*) undergoes *cis*-selective cyclization, dramatic improvement in **c** versus **d** reactivity is observed when the reaction is run at −78 °C under homogeneous conditions (*ii*). Here, *cis*-selectivity improves nearly 2-fold (see Table 1). A variety of electrophiles (iodine monochloride, *N*-bromosuccinimide, and *N*-iodosuccinimide), solvent, and temperature conditions was explored for this electrophilic cyclization, but none led to greater selectivity than those of conditions *ii*.

Dienoic acids **3**–**5** (Figure 2) present the reacting carboxylate with nondiastereotopic olefins since the Cβ- and C′β-positions are differentially substituted. Inspection indicates that acids **3** and **4** present relative stereochemistries paralleling acids **1** and **2**; consequently, the

Table 2. Stereoselectivities in the Iodolactonization of Dienoic Acids 3–5[a]

	Cγ:C′γ	Cγ cis:trans	C′γ cis:trans	combined yield
3 → 8	1:3	3:1	8:1	81%
4 → 9	2:1	3:1	8:1	59%
5 → 10	1:22	--	12:1	74%

[a] Saturated aqueous $NaHCO_3/CH_2Cl_2/I_2$, rt.

two competing olefins should be differentiated by conformational biases analogous to conformations **a** and **b** (Table 1). This allows us to predict that acid **3** should select cyclization onto the C′γ-olefin whereas acid **4** should select cyclization onto the Cγ-olefin. Acid **5** is unique in that the two olefins are nondiastereotopic, but ground-state conformational biases like those of **a** and **b** will not differentiate the two reactive olefins; an a priori prediction of olefin selectivity is not apparent.

Given these observations, we were surprised to find that the room-temperature, two-phase carboxylate ion cyclization of **3** was quite nonselective (Table 2); however, as predicted, iodo lactone **8** was the major product and arose via "*cis*/C′γ-selectivity". Likewise, dienoic acid **4** leads to iodo lactone **9** as the major product but again reflects reduced "*cis*/C′γ-selectivity" when compared to acids **1** and **2**. Correlating the iodolactonization selectivities of these four acids leads to the conclusion that while the same stereocontrol features are operative in each cyclization, the magnitude of selectivity is modulated by subtle nonbonding interactions.

The iodolactonization of dienoic acid **5** gives iodo lactone **10** with high selectivity and underscores the subtlety of these stereocontrol elements. Here, cyclization on either olefin requires a conformation in which the reactive olefin must adopt a high-energy "**b**-like" conformation (see Table 1), and yet C′γ-olefin cyclization occurs with 96% selectivity even though both the Cα–Cβ and Cα–C′β relative stereochemistries are *syn*. In fact, the only difference between the competing olefins in **5** is that Cβ bears an ethyl substituent while C′β bears a methyl substituent. In addition, iodolactonization of **5** proceeds with exceptionally high C4–C5 *cis*-selectivity.

Iodolactonization results with dienoic acids **1**–**5** allow us to conclude that olefin selectivity can be anticipated when the Cα–Cβ/C′β relative stereochemistries differ (i.e., *anti* versus *syn*); in these cases, conformational energy differences between the "**a**-like" versus "**b**-like" conformations depicted in Table 1 favor cyclization toward the *syn*-side olefin (i.e., carboxyl and allylic substituent *syn*). Finally, while the magnitude of both olefin and face selectivity is dramatically mediated by apparently subtle nonbonding interactions, a C4–C5 *cis*-selectivity is observed in all cases, and under no conditions explored were six-membered ring lactones obtained.

Finally, establishing iodo lactone structural and stereochemical assignments proved to be a major part of this

(12) McKew, J. C.; Kurth, M. J. *J. Org. Chem.* **1993**, *58*, 4589–95.

work. Regarding the olefin face selectivity, ^{1}H NMR nuclear Overhauser effect (NOE) measurements between C4H and C5H as well as chemical shift data for C5H proved invaluable in assigning the C4–C5 relative stereochemistries of these iodo lactones. Thus, a *cis*-C4–C5 relationship resulted in a positive C4H·C5H NOE and caused C5H to resonate within a narrow 4.26–4.46 ppm window while a *trans*-C4–C5 relationship resulted in no C4H·C5H NOE but caused C5H to resonate within a narrow 3.83–3.88 ppm window. Regarding the olefin selectivity in these iodolactonization reactions, NOE experiments were required to make structural assigns for the iodo lactones from dienoic acids 1 and 2. With dienoic acids 3-5, straightforward homonuclear ^{1}H NMR decoupling experiments sufficed to determine this parameter. Single-crystal X-ray diffraction analysis of iodo lactones 6 and 8 unambiguously determined the relative stereochemistries of each and, in both cases, verified the stereochemical assignments deduced via ^{1}H NMR experiments.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium–potassium benzophenone ketyl immediately prior to use. Flash chromatography refers to the procedure of Still *et al.*[13] Melting points are uncorrected. Capillary GC refers to use of a DB210 column (30m × 0.25 mm) with H_2 carrier gas at a linear velocity of 44.2 cm/s with the injector port at 220 °C. ^{1}H- and ^{13}C-NMR spectra were measured at 300 and 75 MHz, respectively, and chemical shifts are reported in ppm (internal tetramethylsilane). Mass spectra were obtained with VG TRIO2 (high resolution; VG-11-250 data system) by Dr. A. Dan Jones (Facility for Advanced Instrumentation, University of California, Davis). X-ray crystallographic data were collected on an automated Siemens R3m/V diffractometer, and the structures were solved by direct methods and refined by the full-matrix least-squares method with the aid of SHELXTL PLUS programs.

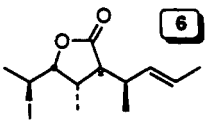
Method A. The dienoic acid (1.0 equiv), dichloromethane (3 mL/mmol of acid), and saturated aqueous sodium bicarbonate (3.0 mL/mmol of acid) were placed in a round-bottom flask equipped with a stir bar. Iodine (1.05 equiv) was added portionwise to this rapidly stirred two-phase reaction mixture, and the reaction was monitored by TLC (dienoic acid generally consumed within 60 min). The excess iodine was quenched by dropwise addition of a saturated aqueous sodium thiosulfate/sodium bicarbonate buffer solution, and then water was added to generate two distinct layers. These layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 15 mL/mmol of acid). The combined organic extracts were washed with a 1 M sodium carbonate solution (1 × 15 mL/mmol of acid) and brine (1 × 15 mL/mmol of acid), dried over potassium carbonate, filtered, and concentrated *in vacuo*. The resulting crude iodo lactones (pale yellow oil) were purified by flash chromatography (silica, 1–8% ethyl acetate/cyclohexane eluent).

Method B. The dienoic acid (1.0 equiv) was weighed into a round-bottom flask which was then sealed with a septum and blanketed with nitrogen, and dry THF (4 mL/mmol of acid) was added. The resulting solution was cooled to −78 °C, n-BuLi (1.05 equiv) was added dropwise, and iodine (1.2 equiv) in dry THF (1.5 mL/mmol of acid) was added dropwise to the reaction vessel. After the solution was stirred 5 h at −78 °C, TLC analysis indicated that the starting dienoic acid had been consumed, the reaction was quenched with saturated aqueous sodium thiosulfate/sodium bicarbonate buffer (2 mL/mmol of acid), and the cooling bath was removed. When the mixture had warmed to room temperature, THF was removed *in vacuo* and the residue was diluted in water (4 mL/mmol of acid). This aqueous layer was extracted with ether (4 × 10 mL/mmol of acid), and the combined organic extracts were washed with brine (1 × 10 mL/mmol of acid), dried over potassium carbonate, filtered, and concentrated *in vacuo*. The resulting crude iodo lactones (pale yellow oil) were purified by flash chromatography (silica, 1–8% ethyl acetate/cyclohexane eluent).

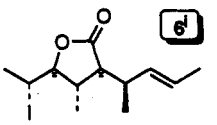
6 and 6^i by Method A. Dienoic acid 1 (230 mg, 1.19 mmol) and iodine (320 mg, 1.25 mmol) yielded a mixture of lactones 6 and 6^i (combined chromatographed yield 280 mg, 73%) which proved to be readily separable by chromatography (4% ethyl acetate/cyclohexane, order of elution being 6 and 6^i). Capillary GC analysis of the crude reaction mixture (100 °C/2 min/2 °C/min, retention times: 6, 19.15 min; 6^i, 21.94 min) established a 7.1:1 ratio of 6:6^i.

6 and 6^i by Method B. Dienoic acid 1 (113 mg, 0.58 mmol), n-BuLi (400 μL of a 1.6M solution in hexanes), and iodine (175 mg, 0.69 mmol) yielded a mixture of lactones 6 and 6^i (combined chromatographed yield 147 mg, 80%). Capillary GC analysis of the crude reaction mixture (100 °C/2 min/2 °C/min, retention times: 6, 19.15 min; 6^i, 21.94 min) established a 11.2:1 ratio of 6:6^i.

6: white solid (from pentane/EtOAc); mp 54–55 °C; $[\alpha]^{20}_D$ = +44.3 (*c* 1.60, EtOH); FT-IR (neat) 2926, 2960, 1774, 1452, 1187 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, *J* = 7.3 Hz, 3H), 1.10 (d, *J* = 5.7 Hz, 3H), 1.66 (d, *J* = 6.3 Hz, 3H), 2.00 (d, *J* = 6.6 Hz, 3H), 2.13 (d, *J* = 8.2 Hz, 1H), 2.39–2.69 (m, 2H) 3.91 (dq, *J* = 10.9, 6.6 Hz, 1H), 4.42 (dd, *J* = 10.9, 5.1 Hz, 1H), 5.24 (dd, *J* = 15.2, 8.3 Hz, 1H), 5.52 (dq, *J* = 15.1, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 17.9, 18.9, 22.5, 25.9, 36.6, 37.3, 56.7, 85.3, 126.9, 132.9, 177.6; HRMS (FAB) calcd for [$C_{12}H_{19}IO_2$ + H] 323.0510, found 323.0503. X-ray crystallographic data for 6 are available through the Cambridge Crystallographic Data Centre.[14]



6^i: yellow oil; $[\alpha]^{20}_D$ = +7.01 (*c* 1.35, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.68 (dd, *J* = 6.3, 1.3 Hz, 3H), 1.94 (d, *J* = 7.0 Hz, 3H), 2.16–2.33 (m, 2H), 2.68–2.84 (m, 1H), 3.83 (t, *J* = 6.4 Hz, 1H), 4.12 (quintet, *J* = 7.0 Hz, 1H), 5.37 (ddq, *J* = 15.4, 7.1, 1.5 Hz, 1H), 5.55 (dq, *J* = 15.4, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9, 18.0, 21.4, 24.1, 27.7, 36.9, 37.0, 54.2, 88.3, 127.0, 132.1, 166.6.



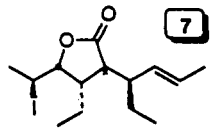
7 and 7^i by Method A. Dienoic acid 2 (220 mg, 0.97 mmol) and iodine (260 mg, 1.02 mmol) yielded a mixture of lactones 7 and 7^i (combined chromatographed yield 330 mg, 95%) which proved to be readily separable by chromatography (2% ethyl acetate/cyclohexane, order of elution being 7 and 7^i). Capillary GC analysis of the crude reaction mixture (100 °C/2 min/2 °C/min, retention times: 7, 30.68 min; 7^i, 32.43 min) established a 3.6:1 ratio of 7:7^i.

7: yellow oil; $[\alpha]^{20}_D$ = +42.7 (*c* 1.35, $CHCl_3$); FT-IR (neat) 2964, 1773, 1186, 996 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (q, *J* = 6.9 Hz, 6H), 1.02–1.06 (m, 1H), 1.26–1.47 (m, 1H), 1.60–1.69 (m, 1H), 1.71 (dd, *J* = 6.4, 1.2 Hz, 3H), 1.73–1.86 (m, 1H), 2.05 (d, *J* = 6.6 Hz, 3H), 2.21–2.39 (m, 2H), 2.42 (d, *J* = 7.3 Hz, 1H), 3.94 (dq, *J* = 11.2, 6.6 Hz, 1H), 4.46 (dd, *J* = 11.1, 5.2 Hz, 1H), 5.13 (ddq, *J* = 15.3, 9.2, 1.3 Hz, 1H), 5.56 (dq, *J* = 15.4, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.2, 11.8, 17.9, 19.2, 22.8, 25.7, 26.0, 43.1, 44.9, 52.1, 85.7, 128.4, 131.0, 178.0; HRMS (FAB) calcd for [$C_{14}H_{23}IO_2$ + H] 351.0823, found 351.0810.

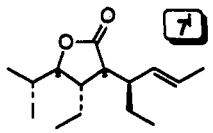
7^i: yellow oil; $[\alpha]^{20}_D$ = −63.05 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.32–1.48 (m, 1H), 1.50–1.65 (m, 3H), 1.67 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.93 (d, *J* = 5.9 Hz, 3H), 2.19–2.28 (m, 1H), 2.32–2.47 (m,

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–5.

(14) The author has deposited atomic coordinates for 6 and 8 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

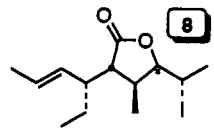


1H), 2.38 (d, J = 4.6 Hz, 1H), 3.93–4.13 (m, 2H), 5.16 (ddq, J = 15.3, 8.5, 1.6 Hz, 1H), 5.53 (dq, J = 15.4, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.7, 12.0, 18.0, 24.5, 25.5, 28.1, 28.3, 42.7, 45.6, 50.5, 87.4, 129.1, 130.9, 177.9.

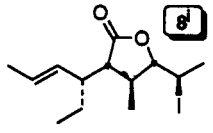


8, 8^{i}, 8^{ii}, and 8^{iii} by Method A. Dienoic acid **3** (470 mg, 2.24 mmol) and iodine (596 mg, 2.35 mmol) yielded a mixture of lactones **8**, **8^{i}**, **8^{ii}**, and **8^{iii}** (combined chromatographed yield 604 mg, 81%; chromatography, 2% EtOAc/cyclohexane, order of elution being **8**/**8^{ii}**, **8^{iii}**, and **8^{i}**). Capillary GC analysis of the crude reaction mixture (100 °C/2 min/2 °C/min, retention times: **8**, 28.55 min; **8^{i}**, 31.13 min; **8^{ii}**, 27.69 min; **8^{iii}**, 29.79 min) established an olefin selectivity (i.e., **8** + **8^{i}**:**8^{ii}** + **8^{iii}**) of 3:1 and facial selectivities of 8.5:1 (**8**:**8^{i}**) and 2.9:1 (**8^{ii}**:**8^{iii}**).

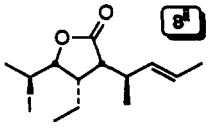
8: white solid (from CH_2Cl_2/hexane); mp 72–72.5 °C; $[\alpha]^{20}_D$ = +33.2 (c 1.05, $CHCl_3$); FT-IR (neat) 2931, 2876, 1778, 1187, 968 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H), 1.28–1.43 (m, 1H), 1.55–1.67 (m, 1H), 1.70 (dd, J = 6.4, 1.5 Hz, 3H), 2.03 (d, J = 6.7 Hz, 3H), 2.22–2.36 (m, 2H), 2.54–2.67 (m, 1H), 3.93 (dq, J = 11.0, 6.6 Hz, 1H), 4.44 (dd, J = 11.0, 5.1 Hz, 1H), 5.14 (ddq, J = 15.2, 8.7, 1.5 Hz, 1H), 5.55 (dq, J = 15.2, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.8, 14.0, 18.0, 22.7, 25.5, 25.9, 36.3 44.8, 55.4, 85.3, 128.8, 130.9, 177.9; HRMS (FAB) calcd for [$C_{13}H_{21}IO_2$ + H] 337.0666, found 337.0683. X-ray crystallographic data for **8** is available through the Cambridge Crystallographic Data Centre.[14]



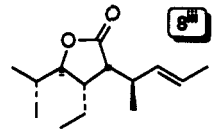
8^{i}: colorless oil; $[\alpha]^{20}_D$ = −31.2 (c 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 1.37–1.62 (m, 2H), 1.67 (dd, J = 6.3, 1.4 Hz, 3H), 1.93 (d, J = 6.9 Hz, 3H), 2.22–2.34 (m, 1H), 2.36 (dd, J = 7.7, 4.4 Hz, 1H), 2.36–2.42 (m, 1H), 3.83 (t, J = 6.6 Hz, 1H), 4.11 (quintet, J = 7.0 Hz, 1H), 5.24 (ddq, J = 15.3, 8.4, 1.5 Hz, 1H), 5.55 (dq, J = 15.3, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.2, 18.2, 21.4, 24.3, 25.2, 27.7, 36.7, 44.6, 53.0, 88.3, 128.8, 130.6, 177.1.



8^{ii}: (note: data are from an inseparable 1:1 mixture of **8**/**8^{ii}**, and some resonances could not be assigned); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.15 (d, J = 6.7 Hz, 3H), 1.71 (dd, J = 6.5, 1.5 Hz, 3H), 2.05 (d, J = 6.6 Hz, 3H), 2.25–2.45 (m, 1H), 2.33 (d, J = 7.6 Hz, 1H), 2.51–2.68 (m, 1H), 3.94 (dq, J = 10.8, 6.4 Hz, 1H), 4.45 (dd, J = 10.9, 5.0 Hz, 1H), 5.26 (ddq, J = 15.2, 8.4, 1.6 Hz, 1H), 5.56 (dq, J = 15.2, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.1, 13.9, 17.9, 19.1, 25.6, 26.0, 37.4, 43.1, 53.1, 85.3, 127.0, 132.8, 178.0.

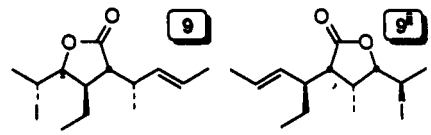


8^{iii}: colorless oil; $[\alpha]^{20}_D$ = −40.4 (c 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.44–1.65 (m, 2H), 1.69 (d, J = 6.1 Hz, 3H), 1.96 (d, J = 6.5 Hz, 3H), 2.14–2.29 (m, 1H), 2.34 (t, J = 5.2 Hz), 2.62–2.78 (m, 1H), 3.96–4.17 (m, 2H), 5.32 (ddq, J = 15.3, 7.5, 1.5 Hz, 1H), 5.56 (dq, J = 15.6, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.8, 17.9, 18.2, 24.4, 28.2, 37.9, 42.8, 51.5, 87.5, 127.2, 132.4, 177.7.

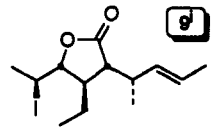


9, 9^{i}, 9^{ii}, and 9^{iii} by Method A. Dienoic acid **4** (198 mg, 0.94 mmol) and iodine (250 mg, 0.99 mmol) yielded a mixture of lactones **9**, **9^{i}**, **9^{ii}**, and **9^{iii}** (combined chromatographed yield 185 mg, 59%; chromatography, 4% EtOAc/cyclohexane, order of elution being **9**/**9^{ii}**, **9^{i}**, and **9^{iii}**). Capillary GC analysis of the crude reaction mixture (100 °C/2 min/2 °C/min, retention times: **9**, 27.69 min; **9^{i}**, 29.69 min; **9^{ii}**, 28.43 min; **9^{iii}**, 31.06 min) established an olefin selectivity (i.e., **9** + **9^{i}**:**9^{ii}** + **9^{iii}**) of 2:1 and facial selectivities of 2.9:1 (**9**:**9^{i}**) and 7.5:1 (**9^{ii}**:**9^{iii}**).

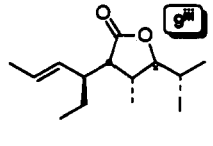
9/**9^{ii}**: (note: data for an inseparable mixture of **9**/**9^{ii}**); yellow oil; FT-IR (neat) 2965, 2929, 2853, 1778, 1671, 1258 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.3 Hz, 6H), 0.97 (d, J = 7.3 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.61–1.66 (m, 6H), 1.97 (d, J = 6.6 Hz, 3H), 1.98 (d, J = 6.6 Hz, 3H), 2.15–2.24 (m, 3H), 2.26 (d, J = 7.6 Hz, 1H), 2.42–2.60 (m, 2H), 3.89 (dq, J = 6.6 Hz, 2H), 4.36–4.45 (m, 2H), 5.09 (ddq, J = 15.1, 5.1, 1.4 Hz, 1H), 5.20 (ddq, J = 15.2, 8.4, 1.5 Hz, 1H), 5.50 (dq, J = 15.2, 6.4, 2H); ^{13}C NMR ($CDCl_3$) δ 11.1, 11.6, 13.9, 14.0, 17.9, 19.0, 19.1, 22.4, 22.6, 25.5, 26.0, 36.3, 37.3, 43.0, 53.1, 55.4, 85.4, 85.7, 126.9, 128.7, 130.9, 132.8, 177.8.



9^{i}: $[\alpha]^{20}_D$ = +42.87 (c 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.46–1.62 (m, 2H), 1.68 (dd, J = 6.2, 0.6 Hz, 3H), 1.95 (d, J = 6.4 Hz, 3H), 2.13–2.27 (m, 1H), 2.33 (t, J = 5.2 Hz, 1H), 2.61–2.78 (m, 1H), 3.96–4.16 (m, 2H), 5.31 (ddq, J = 15.3, 7.6, 1.5 Hz, 3H), 5.57 (dq, J = 15.3, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.8, 17.9, 18.3, 24.5, 28.2, 28.4, 37.9, 42.8, 51.5, 87.5, 127.2, 132.4, 177.6; HRMS (FAB) calcd for [$C_{13}H_{21}IO_2$ + H] 337.0666, found 337.0671.



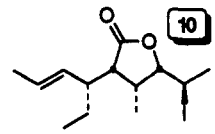
9^{iii}: $[\alpha]^{20}_D$ = +27.29 (c 0.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.27 (d, J = 6.6 Hz, 3H), 1.20–1.35 (m, 2H), 1.68 (dd, J = 6.4, 1.4 Hz, 3H), 1.94 (d, J = 6.9 Hz, 3H), 2.22–2.33 (m, 1H), 2.37 (dd, J = 7.6, 4.3 Hz, 1H), 2.41–2.52 (m, 1H), 3.85 (t, J = 6.6 Hz, 1H), 4.11 (quintet, J = 7.0 Hz, 1H), 5.25 (ddq, J = 15.3, 8.4, 1.6 Hz, 1H), 5.58 (dq, J = 15.4, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 17.9, 18.9, 22.5, 26.0, 36.6, 37.3, 56.8, 85.4, 126.9, 132.9, 177.6.



10 and 10^{i} by Method A. Dienoic acid **5** (180 mg, 0.85 mmol) and iodine (228 mg, 0.90 mmol) yielded a mixture of lactones **10** and **10^{i}** (combined yield 212 mg, 74%). Capillary GC analysis

of the crude reaction mixture (100 °C/2 min/2 °C/min, retention times: **10**, 30.70 min; **10^{i}**, 28.73 min) established an olefin selectivity of 22:1 and facial selectivity of 12:1.

10: white solid (from CH_2Cl_2/cyclohexane); $[\alpha]^{20}_D = -112.8$ (*c* 0.76, $CHCl_3$); FT-IR (neat) 2934, 2876, 1771, 1187, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H), 1.15–1.33 (m, 1H), 1.70 (dd, J = 6.4 Hz, 1.6 Hz, 3H), 2.06 (d, J = 6.6 Hz, 3H), 2.11 (dd, J = 10.0, 2.4 Hz, 1H), 2.21-2.31 (m, 1H), 2.56 (dd, J = 10.6, 6.1 Hz, 1H), 2.62–2.72 (m, 1H), 3.92 (dq, J = 11.1, 6.6 Hz, 1H), 4.26 (dd, J = 11.1, 3.7 Hz, 1H), 5.07 (ddq, J = 15.2, 9.4, 1.6 Hz, 1H), 5.49 (dq, J = 15.2, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.4, 11.2, 18.0, 22.7, 25.4, 25.7, 38.4, 41.2, 50.5, 85.0, 127.5, 131.5, 176.5; HRMS (FAB) calcd for [$C_{13}H_{21}IO_2$ + H] 337.0666, found 337.0661.



Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-9108231) for financial support of this research.

Supplementary Material Available: ^{13}C-NMR spectra for **6**, **6^{i}**, **7**, **7^{i}**, **8**, **8^{i}**, **8^{ii}**/**8**, **8^{iii}**, **9**/**9^{ii}**, **9^{i}**, **9^{iii}**, and **10** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.