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REGIOSELECTIVITY IN THE IODOLACTONIZATION OF 1,6-HEPTADIEN-4-CARBOXYLIC ACID DERIVATIVES

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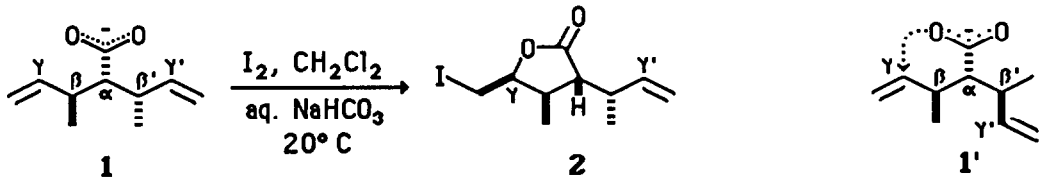
Abstract: Electronic control, as a consequence of differential olefin substitution, and a comparison of conformational versus electronic control in the iodolactonization of 1,6-heptadien-4-carboxylic acid derivatives are reported.

Reactions capable of differentiating similar functionalities within a parent molecule are of considerable importance in synthetic chemistry. Recently, as part of a larger synthetic project, we reported the highly selective kinetic iodolactonization[2] of 1,6-heptadien-4-carboxylic acids -- for example, **1** undergoes iodolactonization to **2** with excellent olefin selectivity (147:1) as well as unprecedented face selectivity (30:1).[3] This olefin selectivity can be rationalized on the basis of acyclic conformational control as a consequence of existing stereocenters. That is, the lowest energy {Cβ→Cα}-Newman projection of **1** places the carboxylate and Cγ'-olefin in close proximity, whereas the lowest energy {Cβ'→Cα}-Newman projection places the carboxylate and Cγ-olefin anti-periplanar. To the extent that a similar bias is experienced in the two transition-states (Cγ- vs. Cγ'-cyclization), carboxylate **1'** is predisposed toward Cγ-cyclization. Herein we report: (i) **electronic control** as a consequence of differential olefin substitution and (ii) a comparison of **conformational** versus **electronic** control in the iodolactonization of 1,6-heptadien-4-carboxylic acid derivatives.

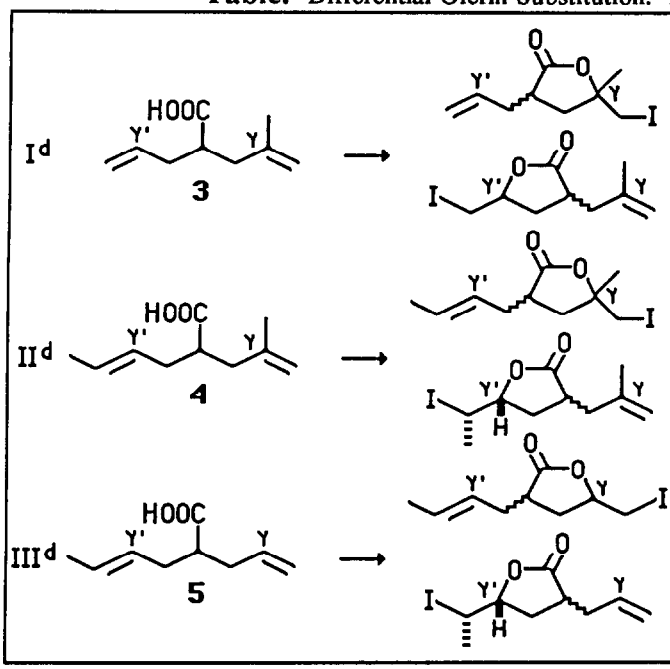


1 **2** **1'**

Acids **3-5** were prepared for the electronic control study as follows. 4-Methyl-2-(2-propenyl)pent-4-enoic acid (**3**)[4] was prepared from dimethyl (2-methyl-2-propenyl)propanedioate[5] by alkylation with allyl bromide (MeONa, MeOH, refulx, 2 h) followed by saponification/decarboxylation (KCN, DMSO, 140°C, 25 h). *E*-2-(2-Methyl-2-propenyl)hex-4-enoic acid (**4**) was prepared by enolate Claisen rearrangement[6] of 2-(3-butenyl) 4-methylpent-4-enoate [(i) LDA, THF, -78°C; (ii) TMSiCl, -78°C→55°C], in turn prepared from 4-

methylpent-4-enoic acid [3-buten-2-ol, DCC, DMAP (cat.), CH_2Cl_2]. Likewise, *E*-2-(2-propenyl)hex-4-enoic acid (**5**)[4] was prepared from 2-(3-butenyl)pent-4-enoate [(i) LDA, THF, -78°C; (ii) TMSiCl, -78°C→ 55°C], in turn prepared from pent-4-enoic acid [3-buten-2-ol, DCC, DMAP (cat.), CH_2Cl_2].

Table. Differential Olefin Substitution: Electronic Control.



	A[a]	B[b]	C[c]
6t[e]	21	150	67
6c[e]	7.1	46	31
7t[f]	2.5	2.5	1.6
7c[f]	1.0	1.0	1.0
% yield[g]	93	96	83
8t[e]	18	23	21
8c[e]	7.4	6.3	5.1
9t[f]	1.1	1.1	1.4
9c[f]	1.0	1.0	1.0
% yield[g]	84	89	80
10t[e]	3.3	2.7	2.5
10c[e]	1.5	1.0	1.0
11t[f]	2.0	1.7	3.6
11c[f]	1.0	1.0	2.4
% yield[g]	85	94	80

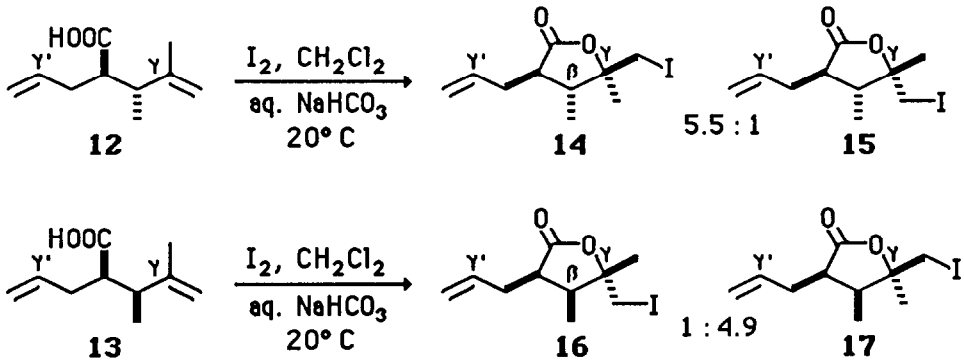
[a]Proc. A: (i) 1 eq. n-BuLi, THF, 20°C; (ii) 3 eq. I_2, 20°C. [b]Proc. B: (i) 1 eq. n-BuLi, THF, -78°C; (ii) 3 eq. I_2, -78°C. [c]Proc. C: 3 eq. I_2, CH_2Cl_2, sat. aq. $NaHCO_3$, 20°C. [d]Ratios determined by capillary GC and/or ^1H NMR. [e]Cis:trans (c:t) stereochemical assignements for **6**, **8**, and **10** were made on the basis of spectral data.[7] [f]Cis:trans (c:t) stereochemical assignements for **7**, **9**, and **11** were tentatively made in analogy with **6**, **8**, and **10**. [g]Combined yields for the four diastereomers.

Several trends are apparent upon inspection of the **Table**. First, the methallyl moiety in **3** and **4** is a powerful director: selectivity ranges from 8:1 (entry I•A) to 56:1 (entry I•B) in favor of the methallyl moiety. Second, there is little allyl versus crotyl selectivity in **5**: selectivity ranging from marginal allyl selectivity (1.6:1; entry III•A) to marginal crotyl selectivity (1:1.7; entry III•C). Third, the three kinetic iodolactonization conditions employed gave the major iodolactones (**6**, **8**, and **10**) with 2 to 4:1 trans:cis selectivity.[2] Finally, the chemical yields for these iodolactonization reactions are excellent.

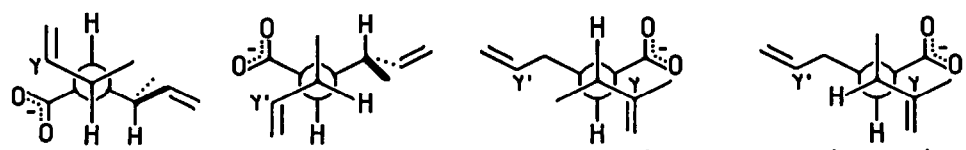
In light of these electronic control experiments and our previous conformational control experiments, an interesting question arises: which control element is dominant in the kinetic iodolactonization of 1,6-heptadien-4-carboxylic acids? To address this question, we chose as substrates dienoic acids **12** and **13**. *Threo* 3,4-dimethyl-2-(2-propenyl)pent-4-enoic acid (**12**)[8] was prepared by enolate Claisen rearrangement[6] of *E*-2-methylbut-2-enyl pent-4-enoate [(i) LDA, 77:23 THF:HMPA, -78°C; (ii) TMSiCl, -78°C→55°C], in

turn prepared from pent-4-enoic acid [*E*-2-methylbut-2-enol, DCC, DMAP (cat.), CH_2Cl_2]. Likewise, *erythro* 3,4-dimethyl-2-(2-propenyl)pent-4-enoic acid (**13**)[9] was prepared by enolate Claisen rearrangement[6] of *E*-2-methylbut-2-enyl pent-4-enoate [(i) LDA, THF, -78°C; (ii) TMSiCl, -78°C→ 55°C].

The kinetic iodolactonization results with **12** and **13** are depicted below. Two important observations are immediately apparent. First, regardless of the syn/anti nature of the starting 1,6-heptadien-4-carboxylic acid, kinetic iodolactonization is highly methallyl selective indicating that, with these substrates, electronic control completely dominates over conformational control. Second, factors controlling Cγ relative asymmetric induction are apparantly quite subtle as **12** and **13** both undergo Cγ-*re* selective addition: thus, **12** favors a *trans* Cβ-CH_3•Cγ-CH_2I relationship (**14**:**15**::5.5:1) while **13** favors a *cis* Cβ-CH_3•Cγ-CH_2I relationship (**16**:**17**::1:4.9).[10] In contrast, all three stereoisomers of **1** (*anti•syn*, *anti•anti*, and *syn•syn*) undergo kinetic iodolactonization favoring a *cis* Cβ-CH_3•Cγ-CH_2I relationship.



Olefin selectivity in the iodolactonization of **1** was rationalized on the basis of conformational control.[3] Similarly, minimizing gauche interactions,[11] the lowest energy {Cβ→Cα}-Newman projection of **12** places the carboxylate and Cγ-olefin (methallyl) in close proximity whereas the lowest energy {Cβ→Cα}-Newman projection of **13** places the carboxylate and Cγ-olefin (methallyl) anti-periplanar. Thus, conformational control, which clearly differentiates the Cγ•Cγ' olefins in **1** (147:1 selectivity), presumably favors methallyl cyclization in **12**, but does not disfavor methallyl cyclization in **13**.



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References and Notes:

1 Sloan Foundation Fellow, 1987-1989.

2 (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. (b) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625. (c) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. (d) Gonzàlez, F. B.; Bartlett, P. A. *Org. Synth.* **1985**, *64*, 175.

3 Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844.

4 Atkinson, R. S.; Malpass, J. R.; Skinner, K. L.; Woodthorpe, K. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1905.

5 Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**,*41*, 1347.

6 Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

7 (a) Spectral data for **8-trans**: IR (neat) 1773 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.52 (s, 3H), 1.62 (d, J = 6.2 Hz, 3H), 1.92 (dd, J = 11.0 and 13.1 Hz, 1H), 2.21 (dd, J = 9.3 and 13.1 Hz, 1H), 2.23 (m, 1H), 2.47 (m, 1H), 2.80 (m, 1H), 3.34 (d, J = 10.6 Hz, 1H), 3.34 (d, J = 10.7 Hz, 1H), 5.42 (m, 2H); NOESY: strong positive NOE between the C(3)-H and the C(5)-CH_2I; ^{13}C-NMR ($CDCl_3$) δ 15.2, 17.9, 25.0, 33.1, 38.8, 40.1, 81.4, 126.7, 128.6, 176.9; calcd for $C_{10}H_{15}O_2I$, 294.0118; found, 294.0115. (b) ^{13}C-NMR data for **8-cis**: ($CDCl_3$) δ 14.0, 17.9, 27.6, 33.9, 37.9, 41.0, 82.0, 126.5, 128.9, 177.4; ^{13}C-NMR data for **6-trans**: ($CDCl_3$) δ 15.2, 25.0, 34.3, 39.0, 40.3, 81.5, 117.9, 134.3, 176.8; ^{13}C-NMR data for **6-cis**: ($CDCl_3$) δ 13.7, 27.6, 35.1, 38.0, 40.5, 82.1, 118.1, 134.1, 177.2.

8 Pure *threo* acid **12** was obtained as follows: enolate Claisen rearrangement of the Z-silylketene derived from *E*-2-methylbut-2-enyl pent-4-enoate (THF:HMPA) gave a 78:22 mixture of **12** and **13**, respectively. Subsequent iodolactonization produced a mixture of iodolactones which were purified by medium pressure LC (85:15::hexane:ethyl acetate, EM Lobar^{TM} SiO_2 column, ca. 30 psi). The major lactone (**14**) was retrolactonized (3 eq. Zn, HOAc, Et_2O, 25°C) giving pure *threo* **12**.

9 Pure *erythro* acid **13** was obtained as follows: enolate Claisen rearrangement of the *E*-silylketene derived from *E*-2-methylbut-2-enyl pent-4-enoate (THF) gave a 19:81 mixture of **12** and **13**, respectively. Subsequent iodolactonization produced a mixture of iodolactones which were purified by medium pressure LC (85:15::hexane:ethyl acetate, EM Lobar^{TM} SiO_2 column, ca. 30 psi). The major lactone (**16**) was retrolactonized (3 eq. Zn, HOAc, Et_2O, 25°C) giving pure *erythro* **13**.

10 Spectral data for **16**: IR (CCl_4) 1772 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.98 (d, J = 7.3 Hz, 3H), 1.53 (s, 3H), 2.21 (m, 1H), 2.57 (dt, J = 15.4 and 1.6 Hz, 1H), 2.78 (q, J = 7.3 Hz, 1H), 2.94 (m, 1H), 3.37 (s, 2H), 5.13 (m, 2H), 5.84 (m, 1H); NOESY: strong positive NOE between the C(4)-Me and the C(5)-Me; ^{13}C-NMR ($CDCl_3$) δ 11.3, 12.6, 22.4, 29.8, 38.0, 43.0, 85.0, 117.0, 136.0, 177.0; calcd for $C_{10}H_{15}O_2I$, 294.0117; found, 294,0091.

11 Kingsbury, C. A. *J. Chem. Ed.* **1979**, *56*, 431, and references therein.

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