Assigning the Relative Stereochemistry between C(2) and C(4) of the 2-Acetonyl-4-alkylbutyrolactone Substructures of the Appropriate Annonaceous Acetogenins

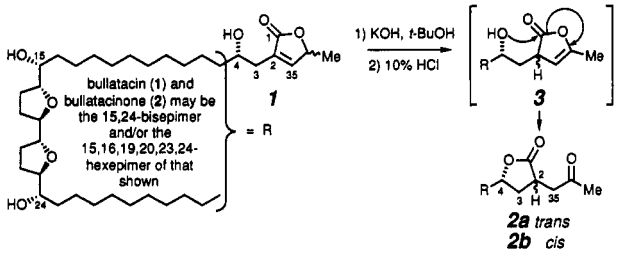
Thomas R. Hoye* and Paul R. Hanson[1]

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received February 19, 1991

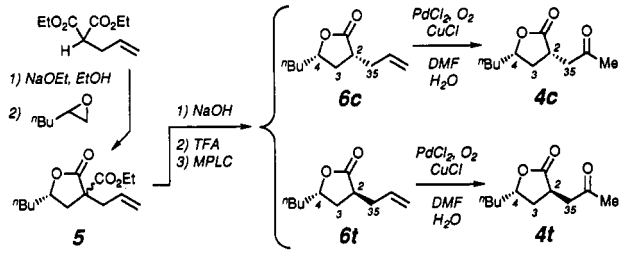
The relative stereochemistry between C(2) and C(4) of the naturally occurring, rearranged acetonylbutyrolactone-containing annonaceous acetogenins has been determined. Model lactones **4c**, **4t**, **6c**, and **6t**, which mimic the rearranged portion of the natural products in question, have been synthesized and unambiguously assigned as having cis or trans stereochemistry on the basis of ^{1}H NMR NOE experiments. Each stereoisomeric pair displays diagnostic coupling constant and chemical shift trends. These data were then compared with those of all of the pertinent acetogenins bullatacinone (**2**), squamone (**7**), isoannonacin (**8**), isoannonacin-10-one (**9**), and rollinone (**10**) and some of their peracetate derivatives. For none of these compounds had the C(2)/C(4) relative stereochemistry been previously determined. The major (for **2** and **10**) or only reported isomers (for **7**–**9**) bear a trans C(2)/C(4) relationship.

Since the report of the discovery of uvaricin in 1982,[2] the class of related, naturally occcurring annonaceous acetogenins has rapidly grown to now include approximately 30 members.[3] Among the more recently discovered structures within the class are those containing either a C(4)-hydroxyl group as exemplified by bullatacin (**1**)[4] or the rearranged acetonylbutyrolactone moiety present in bullatacinone (**2**).[4] Although both trans and cis isomers



of **2** have been isolated directly by fractionation of natural material, **1** can be chemically transformed into a mixture of **2a** and **2b**,[4a] presumably by way of either a translactonization event or saponification/relactonization of the intermediate butenolide isomer **3**. Given the increasing number of examples of these "rearranged" ketolactones,[4,5] the biological interest of the series in general,[3] and our experience in defining certain stereochemical issues within various substructural units of these acetogenins,[6] we decided to develop a protocol that would allow for the assignment of the relative stereochemistry between positions C(2) and C(4) of the lactone ring (bullatacinone skeleton numbering is used throughout for all synthetically prepared compounds).

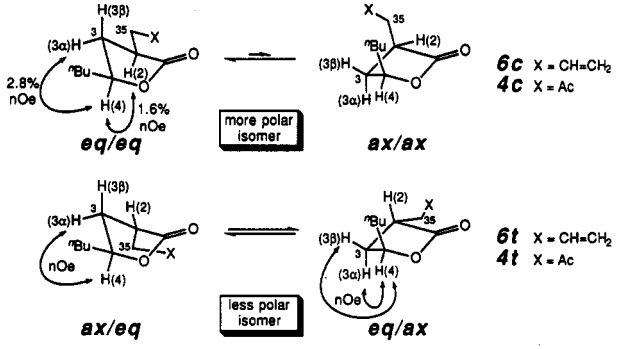
The successful strategy used in our solution to the general problem of assignment of relative stereochemistry within the bis(tetrahydrofuranyl) [C(15)–C(24)] moiety of the acetogenins involved synthesis of a suitable array of model compounds of known stereochemistry and subsequent, detailed comparison of their ^{1}H NMR characteristics with those of the natural products. In a similar manner we chose to synthesize and prove the structure of the model cis- and trans-substituted 2-acetonyl-4-butyl-γ-butyrolactones (**4c** and **4t**) for eventual spectroscopic correlation. Thus, malonic ester synthesis of the lactones **5** was achieved by reaction of diethyl sodioallylmalonate with 1-hexenoxide. Decarbethoxylation of this mixture gave the 2-allyl-4-butyl-γ-butyrolactones (**6c** and **6t** in an ~1:1 ratio), which were separated by chromatography on silica gel. Finally, each individual isomer was oxidized to its methyl ketone (**4c** and **4t**) under Wacker conditions.[7]



With these appropriate model compounds in hand and knowing that the isomers of each diastereomeric pair gave distinguishing ^{1}H (and ^{13}C) NMR spectroscopic data, we deemed it necessary to unambiguously assign the relative configuration within each pair of isomeric lactones **4** and **6**. Thus, both isomers of **6** were studied by difference NOE spectroscopy.[8] Enhancements in the more polar (SiO_2) isomer between proton pairs H(4)/H(2) (1.6%) and H(4)/H(3α) (2.8%) and in the less polar isomer between H(4) and both H(3α) and H(3β) (total enhancement of 2.9%) but, significantly, *not* between H(4) and H(2) allowed the assignment of the cis (**6c**) and trans (**6t**) stereochemistries to the more and less polar isomers, respectively. This relative elution behavior (as well as ^{1}H NMR data, vide infra) is consistent with that observed for a set of four cis/trans isomeric pairs of 2,4-dialkyl(or phenylalkyl)-γ-butyrolactones described by Ollis.[9]

(1) 3M Graduate Fellow, 1990–91.
(2) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R. *J. Org. Chem.* **1982**, *47*, 3151.
(3) For a recent and very useful review, see: Rupprecht, J. K.; Hui, Y. H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237.
(4) (a) Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463. (b) Lix, X. H.; Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Wood, K. V.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 81.
(5) (a) Squamone.[4b] (b) Isoannonacin and isoannonacin-10-one: Xu, L. Z.; Chang, C. J.; Yu, J.; Cassady, J. M. *J. Org. Chem.* **1989**, *54*, 5418. (c) Rollinone: Abreo, M. J.; Sneden, A. T. *J. Nat. Prod.* **1990**, *53*, 983.
(6) (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4402. (b) Hoye, T. R.; Zhuang, Z. *J. Org. Chem.* **1988**, *53*, 5578. (c) Studies for determining the relative configuration between C(4) and C(36) of the 4-hydroxy acetogenins (e.g., **1**) are in progess.
(7) E.g., Tsuji, J. *Synthesis* **1984**, 369.
(8) Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 277.

0022-3263/91/1956-5092$02.50/0



Meaningful and diagnostic trends in the proton chemical shift data were evident for cis and trans isomers of both the allylated lactones **6c** and **6t** and their acetonyl congeners **4c** and **4t** (see Table I). These trends are summarized in Chart I. Particularly noteworthy are that in the pair of trans-substituted lactones: (i) the methine proton H(4) is farther downfield, (ii) the difference in chemical shift ($\Delta\delta$) for the H(3) geminal pair of protons is smaller, and (iii) the coupling constant between H(4) and H(3β) is considerably smaller. This last fact is consistent with the predominance of the eq/eq conformer in the cis isomers but with significant populations of both ax/eq and eq/ax conformers in the trans lactones.[9]

Available ^{1}H NMR data for the natural products bullatacinone (**2**),[4a] squamone (**7**),[4b] isoannonacin (**8**),[5b] isoannonacin-10-one (**9**),[5b] rollinone (**10**),[5c] and some of their peracetate derivatives are summarized in Table II. The solvent and field strength for the NMR measurements are noted in the headings. Comparison of the chemical shift for the lactone methine proton, H(4), in both $CDCl_3$ and C_6D_6 for all of these compounds (except **2b** and **10b**) shows that the chemical shifts of δ 4.545 ($\pm$0.015) in $CDCl_3$ and δ 4.025 ($\pm$0.025) in C_6D_6 correspond favorably with those of the trans-substituted model compound **4t** (δ 4.55 and 4.02, respectively, Table I). Alternatively, the chemical shift of proton H(4) in compounds **2b** (δ 3.72, C_6D_6) and **10b** (δ 4.39, $CDCl_3$) corresponds well with that of the cis-substituted model compound **4c** [δ 3.69 (C_6D_6) and 4.41 ($CDCl_3$)]. Numerous sets of coupling constants for individual protons also show strong correlation between the natural products (except isomers **2b** and **10b**) and the trans-substituted lactone **4t**. One particularly compelling example of this fact is the multiplicity observed for proton H(3β) in **4t** as well as all of the compounds in Table II (except **2b** and **10b**); each contains, in addition to a $J_{gem[3(\alpha)]}$, one large and one small coupling constant to the vicinal neighbors H(2) and H(4), respectively. In other words the H(3β) resonance lacks the two large trans-diaxial coupling constants which are present in the cis-substituted compound **4c**.

Taken collectively, the above arguments allow the confident assignment of the relative stereochemistry between stereocenters C(2) and C(4) in the natural products bullatacinone isomer **2a**, squamone (**7**), isoannonacin (**8**), isoannonacin-10-one (**9**), and rollinone isomer **10a** as well as in their acetate derivatives **2a-Ac**, **7-Ac**, **8-Ac**, and **9-Ac** as trans. The relative configuration in bullatacinone isomer **2b** and in rollinone isomer **10b** is cis. We propose here the use of the stereochemical modifiers "cis" and "trans", as appropriate, to precede the name of those natural products for which both C(2)/C(4) diastereomers have been characterized (i.e., **2a** is *trans*-bullatacinone,[4a] **2b** is *cis*-bullatacinone, **10a** is *trans*-rollinone,[5c] and **10b** is *cis*-rollinone[5c]). We are continuing to probe additional stereochemical issues within the entire series of natural tetrahydrofuran-containing acetogenins.

(9) (a) Tayyeb Hussain, S. A. M.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1480. (b) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6758. (c) Klun, T. P. Ph.D. Thesis, University of Wisconsin at Madison, 1981.

Table I. ^{1}H NMR Chemical Shifts[a] and Coupling Constants of the Core Protons in the Cis and Trans Disubstituted Allyl and Acetonyl Lactones 6c, 4c, 6t, and 4t

proton $J_{i,j}$ (Hz)	compound no. 6c	4c	6t	4t
H(2)	δ 2.71 (dddd)	δ 3.03 [2.61] (dddd)	δ 2.72 (dddd)	δ 3.02 [2.70] (dddd)
$J_{2,3\beta}$	12.7	11.7	9.3	9.8[b]
$J_{2,3\alpha}$	8.8	8.6	7.8	8.8[b]
$J_{2,35a}$	7.8	8.6	8.7	9.3[b]
$J_{2,35b}$	3.9	3.9	4.9	3.4[b]
H(3α)	δ 2.41 (ddd)	δ 2.59 [1.98] (ddd)	δ 2.10[c] (ddd)	δ 2.01[c] [1.37][c] (ddd)
$J_{3\alpha,3\beta}$	12.2	11.7	12.7	13.7
$J_{3\alpha,4}$	5.4	5.9	7.8	8.8
H(3β)	δ 1.55 (ddd)	δ 1.50 [0.88] (ddd)	δ 2.02[c] (ddd)	δ 2.23[c] [1.68][c] (ddd)
$J_{3\beta,4}$	10.7	9.8	5.9	3.9
H(4)	δ 4.35 (dddd)	δ 4.41 [3.69] (dddd)	δ 4.48 (dddd)	δ 4.55 [4.02] (dddd)
$J_{4,5a/b}$	7.7/5.4	7.8/5.4	7.3/5.4	8.1/5.8
H(35a)	δ 2.24 (ddd)	δ 2.64 [1.91] (dd)	δ 2.27 (ddd)	δ 2.69 [1.96] (dd)
$J_{35a,35b}$	14.8	18.0	13.6	19.0
H(35b)	δ 2.63 (ddd)	δ 3.09 [2.64] (dd)	δ 2.56 (ddd)	δ 3.03 [2.54] (dd)
H(37)		δ 2.20 [1.59] (s)		δ 2.20 [1.58] (s)

[a] Data are reported for $CDCl_3$ solutions of **4** and **6** except for the chemical shifts in brackets which are for C_6D_6 solutions. [b] Coupling constants for this multiplet identified from the spectrum recorded in C_6D_6. [c] The assignments of α vs β may be reversed for the trans series.

Experimental Section

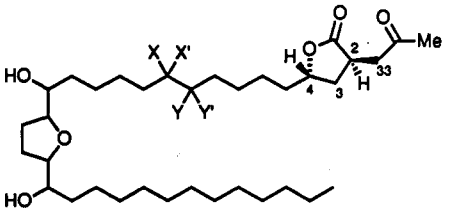
Mixture of (±)-*cis*- and (±)-*trans*-2-(Ethoxycarbonyl)-2-(2-propenyl)-γ-octanoic Lactones (5). Sodium (1.15 g, 49.9 g·atoms) was carefully added to absolute ethanol (50 mL) under a nitrogen atmosphere. After hydrogen evolution had stopped, diethyl allylmalonate (10.0 g, 9.85 mL, 49.9 mmol) was added dropwise. The light brown homogeneous solution was stirred at rt for 30 min, and 1-hexenoxide (7.23 mL, 60.0 mmol) was added dropwise. The resulting mixture was stirred at 55–60 °C for 48 h and quenched with 200 mL of 10% KH_2PO_4. After extraction with $CHCl_3$ (3×) the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to leave 12.1 g (95%) of crude product. Distillation (97–98 °C, at ~0.50 mmHg) gave 8.06 g of a mixture comprised mostly of the decarbethoxylated products, **6c** and **6t**, along with some of **5** (~10–30% ^{1}H NMR analysis). This crude material was further processed into pure **6c** and **6t** as described below.

(±)-*cis*- and (±)-*trans*-2-(2-Propenyl)-γ-octanoic Lactone (6c and 6t). Ester lactones **5** (8.1 g, 31.7 mmol) were heated at reflux with KOH/H_2O (4.4 g, 79.1 mmol in 62 mL) for 48 h. The cooled mixture was washed with Et_2O (2×). The remaining aqueous phase was concentrated under reduced pressure to yield a brown solid to which TFA (18 mL) was cautiously added with swirling to yield a brown homogeneous solution. After 5 min the solution was concentrated under reduced pressure, and the residue was triturated with CH_2Cl_2 and filtered. The filtrate was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 5.0 g (87%) of a crude yellow oil. MPLC (23:1, Hex–EtOAc) of 600 mg of this crude material gave 164 mg of a faster eluting trans isomer (24%) and 214 mg of a slower eluting cis/isomer (31%). **6c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dddd, 1 H, J = 17.1, 9.8, 6.8, 6.8 Hz, C*H*=CH_2), 5.12 (dd, 1 H, J = 16.7, 2.0 Hz, CH=CH_aH$_b$), 5.09 (dd, J = 9.8, 2.0 Hz, CH=CH$_a$*H*$_b$), 4.35 (dddd, 1 H, J = 10.7, 7.7, 5.4, 5.4 Hz, C*H*OCO), 2.71 (dddd, 1 H, J = 12.7, 8.8, 7.8, 3.9 Hz, C*H*CO_2), 2.63, (ddd, J = 14.8, ~6, ~4 Hz, CH_aH$_b$CH=CH_2), 2.41 (ddd, J = 12.2,

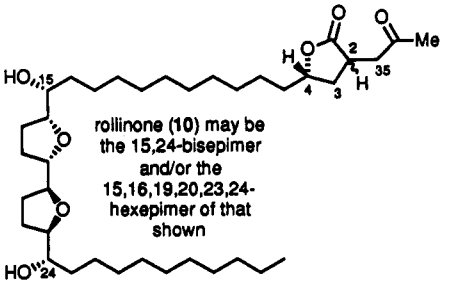
Chart I. Diagnostic ^{1}H NMR Spectroscopic Trends for the *cis*- and *trans*-Lactones 4 and 6 (in $CDCl_3$)

cis isomers (6c and 4c)	vs	*trans* isomers (6t and 4t)
$\delta_{H(4)}$ farther upfield (4.35 and 4.41)	(i)	$\delta_{H(4)}$ farther downfield (4.48 and 4.55)
$\Delta\delta_{H(3\beta)/H(3\alpha)}$ larger (~1 ppm)	(ii)	$\Delta\delta_{H(3\beta)/H(3\alpha)}$ smaller (≤0.2 ppm)
$J_{3\beta,4}$ = larger (~10 Hz)	(iii)	$J_{3\beta,4}$ = smaller (~4.5 Hz)
$\Delta\delta_{H(35a)/H(35b)}$ slightly larger (0.4–0.5 ppm)	(iv)	$\delta\Delta_{H(35a)/H(35b)}$ slightly smaller $\Delta\delta$ (0.2–0.3 ppm)
$J_{2,3\beta}$ = larger (~12 Hz)	(v)	$J_{2,3\beta}$ = smaller (~9 Hz)

Table II. ^{1}H NMR Chemical Shifts and Coupling Constants of the Lactone Core Protons in Bullatacinone Diacetate [2a-Ac],[a] Bullatacinone isomers (2a[a] and 2b,[a] C_6D_6), Squamone (7, C_6D_6),[b] Squamone Diacetate (7-Ac),[b] Isoannonacin (8),[b] Isoannonacin Triacetate (8-Ac),[b] Isoannonacin-10-one (9),[b] Isoannonacin-10-one Diacetate (9-Ac),[b] Isomers[b] Rollinone Isomers[b] (10a and 10b)[b]



		X, X'	Y, Y'
7	squamone	H, H	=O
8	isoannonacin	H, OH	H, H
9	isoannonacin-10-one	=O	H, H



10a *trans*-rollinone H(2) is "down"
10b *cis*-rollinone H(2) is "up"

proton	2a-Ac ($CDCl_3$, 470 MHz)	2a (C_6D_6, 470 MHz)	2b[a] (C_6D_6, 470 MHz)	7 (C_6D_6, 500 MHz)	7-Ac ($CDCl_3$, 200 MHz)	8 ($CDCl_3$, 470 MHz)	8-Ac ($CDCl_3$, 470 MHz)	9 ($CDCl_3$, 470 MHz)	9-Ac ($CDCl_3$, 470 MHz)	10a[b] ($CDCl_3$, 500 MHz)	10b[b] ($CDCl_3$, 500 MHz)
H(2)	δ 3.02 (*J* = 12.8, 9.3, 9.3, 3.4)	δ 2.71 (*J* = 9.3, 9.3, 9.3, 3.4)	δ 2.62 (dddd)	δ 2.69 (*J* = 9.2, 9.2, 9.2, 3.5)	δ 3.05	δ 3.02[d] (*J* = 17, 9.5, 9.0, 3.6)[d]	δ 3.03[d] (*J* = 17, 9.5, 9.0, 3.6)[d]	δ 3.03[d] (*J* = 17, 9.5, 9.0, 3.6)[d]	δ 3.03[d] (*J* = 17, 9.5, 9.0, 3.6)[d]	δ ~3.0 (m)	δ ~3.0 (m)
H(3$_\alpha$)	δ 2.00 (m)	δ 1.40	δ 1.95	δ 1.65[e] (m)		δ 1.96 (m)	δ 1.96 (m)	δ 1.99 (m)	δ 1.96 (m)	δ 1.99 (*J* = 13, 9, 9)	δ 2.61 (m)
H(3$_\beta$)	δ 1.74[e] (m)	δ 1.70 (*J* = 12.8, 9.3, 3.4)	δ 0.87	δ 1.65[e] (m)		δ 2.23 (*J* = 9.5, 9.0, 3.6)[f]	δ 2.23 (*J* = 9.5, 9.0, 3.6)[f]	δ 2.23 (*J* = 9.5, 9.0, 3.6)[f]	δ 2.23 (*J* = 9.5, 9.0, 3.6)[f]	δ 2.24 (*J* = 12.7, 9.8, 3.4)	not observable
H(4)	δ 4.53	δ 4.05 (m)	δ 3.72 (m)	δ 4.00 (*J* = 8.2, 8.2, 4.9, 3.4)	δ 4.56	δ 4.54 (*J* = 7.0, 7.0, 4.3, 3.6)	δ 4.55 (*J* = 7.0, 7.0, 4.3, 3.6)	δ 4.55 (*J* = 7.0, 7.0, 4.3, 3.6)	δ 4.54 (m)	δ 4.55 (*J* = 8.0, 8.0, 5.9, 3.5)	δ 4.39 (*J* = 10.7, 7.0, 5.8, 5.8)
H(35a)[c]	δ 2.66 (*J* = 18.3, 9.3)	δ 1.93 (*J* = 18.3, 9.3)	δ 1.89 (dd)	δ 1.91 (*J* = 18.4, 9.2)	δ 2.68	δ 2.66 (*J* = 17, 9.5)	δ 2.68 (*J* = 17, 9.5)	δ 2.68 (*J* = 17, 9.5)	δ 2.68 (*J* = 17, 9.5)	δ 2.67 (*J* = 18.5, 8.8)	δ 2.60 (*J* = 18.5, 8.8)
H(35b)[c]	δ 3.04 (*J* = 18.3, 3.4)	δ 2.53 (*J* = 18.3, 3.4)	δ 2.64 (dd)	δ 2.51 (*J* = 18.4, 3.5)	δ 3.04	δ 3.01[d] (*J* = 9.5, 9.0)[d]	δ 3.01[d] (*J* = 9.5, 9.0)[d]	δ 3.01[d] (*J* = 9.5, 9.0)[d]	δ 3.01[d] (*J* = 9.5, 9.0)[d]	δ 3.04 (*J* = 19, 3)	δ 3.11 (*J* = 19.0, 3.4)
H(37)[c]	δ 2.20	δ 1.55	δ 1.56	δ 1.54	δ 2.20	δ 2.20	δ 2.20	δ 2.20	δ 2.20	δ 2.20	δ 2.20

[a] Unpublished data provided by Professor J. McLaughlin and Y. H. Hui. [b] Data recorded for a naturally occurring sample provided by Professor A. Sneden and M. Abreo containing an ~1:1 mixture of the cis and trans diastereomers. [c] C(35) and C(37) in 2 and 10 (bis-THF compounds) correspond to C(33) and C(35), respectively, in 7, 8, and 9 (mono-THF compounds). [d] Because of the near superposition of the multiplets for H(33b)[c] and H(2) in spectra recorded in $CDCl_3$, these assignments—reported here as found in the original paper—are not entirely correct. Namely, (1) the $J_{gem(33a/33b)}$ of 17 Hz which is observed in the H(33a) multiplet should also be present in the H(33b) multiplet [rather than in the H(2) multiplet] and (2) $J_{2/33a}$ of ~3.5 Hz should be mirrored in both multiplets. That is, H(33b) is likely a dd with *J* = 17 and 3.5 Hz [cf., H(35b)[b] in 2 and 10]. [e] These assignments are suspect since they fall among the resonances for many other protons in the molecule. [f] The correct assignment of the *J* values for this multiplet is suspect (i.e., $J_{gem[H(3\alpha/3\beta]}$ ~12–13 Hz is absent; cf. H(3β) in 10a and 4t).

8.8, 5.4 Hz, C*H*$_a$CH$_b$CHCO$_2$), 2.24 (ddd, *J* = 14.8, 8.8, 6.8 Hz, CH$_a$*H*$_b$CH=CH$_2$), 1.75 (m, 1H, CH$_2$C*H*$_a$CH$_b$CHOCO), 1.60 (dddd, 1 H, *J* = 9.7, 7.7, 5.4, 5.4 Hz, CH$_2$CH$_a$C*H*$_b$CHOCO), 1.55 (ddd, 1 H, *J* = 12.7, 12.2, 10.7 Hz, CH$_a$C*H*$_b$CHCO$_2$), 1.44 (m, 1 H, CH$_3$CH$_2$C*H*$_a$CH$_b$), 1.35 (m, 3 H, CH$_3$C*H*$_2$CH$_a$C*H*$_b$), 0.92 (t, 3 H, *J* = 6.8 Hz, C*H*$_3$); ^{13}C NMR (75 MHz, assignments confirmed by reverse-detection ^{1}H/^{13}C HETCOR experiment) δ 178.07 C(1), 134.52 C(36), 117.28 C(37), 78.86 C(4), 40.44 C(2), 35.08, 34.37, 34.17, 27.23, 22.30, 13.76 C(8); IR (neat) 3079, 2933, 2863, 1770, 1642, 1457, 1354, 1308, 1181, 1004, 921 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.09; H, 9.81. **6t**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (dddd, 1 H, *J* = 17.6, 9.8, 6.8, 6.8 Hz, C*H*=CH$_2$), 5.14 (dd, 1 H, *J* = 15.6, 2.0 Hz, CH=C*H*$_a$H$_b$), 5.11 (dd, *J* = 10.8, 2.0 Hz, CH=CH$_a$*H*$_b$), 4.48 (dddd, 1 H, *J* = 7.3, 7.3, 5.4, 5.4 Hz, C*H*OCO), 2.72 (dddd, 1 H, *J* = 9.3, 8.7, 7.8, 4.9 Hz, C*H*CO$_2$), 2.56 (ddd, *J* = 13.7, 6.8, 4.9 Hz, C*H*$_a$H$_b$CH=CH$_2$), 2.27 (ddd, *J* = 13.6, 8.7, 7.8 Hz, CH$_a$*H*$_b$CH=CH$_2$), 2.10 (ddd, *J* = 12.7, 7.8, 7.8 Hz, C*H*$_a$CH$_b$CHCO$_2$), 2.02 (ddd, 1 H, *J* = 12.7, 9.8, 5.9 Hz, CH$_a$C*H*$_b$CHCO$_2$), 1.70 (m, 1 H, CH$_2$C*H*$_a$CH$_b$CHOCO), 1.56 (m, 1 H, CH$_2$CH$_a$C*H*$_b$CHOCO), 1.41 (m, 1 H, CH$_3$CH$_2$C*H*$_a$CH$_b$), 1.35 (m, 3 H, CH$_3$C*H*$_2$CH$_a$C*H*$_b$), 0.92 (t, 3 H, *J* = 6.8 Hz, C*H*$_3$); ^{13}C NMR (75 MHz) δ 178.70, 134.39, 117.68, 78.80, 38.91, 35.28, 34.80, 32.53, 27.33, 22.32, 13.82; IR (neat) (on mixture) 3079, 2933, 2863, 1770, 1642, 1457, 1354, 1308, 1181, 1004, 921 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.14; H, 9.86.

(±)-*cis*-2-(2-Oxopropyl)-γ-octanoic Lactone (4c). To a stirred solution of cuprous chloride (CuCl, 255 mg, 2.58 mmol) and $PdCl_2$ (46 mg, 0.26 mmol, 10 mol %) in 4.0 mL of DMF in a 10-mL two-neck round-bottomed flask fitted with a bubbler and septum was added 0.5 mL of water. Oxygen was bubbled through the solution for 1.5 h, and alkene **6c** (470 mg, 2.58 mmol) in 1 mL of DMF was then added via syringe. After 40 h the reaction mixture was partitioned between water and Et_2O, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×). The organic layers were combined, washed with brine, filtered through an alumina plug, and concentrated under reduced pressure, leaving a crude yellow oil (514 mg, 101%). MPLC (3:1 Hex–EtOAc) gave 440 mg (86%) of a clear product that contained <10% of the corresponding terminal aldehyde. For detailed spectroscopic analysis, a sample of 4c contaminated with its isomeric aldehyde was taken up in CH_2Cl_2, washed with a saturated solution of $NaHSO_3$, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to leave pure 4c (~80% recovery): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (dddd, 1 H, *J* = 9.8, 7.8, 5.9, 5.4 Hz, C*HOCO*), 3.09 (dd, 1 H, *J* = 18.1, 3.4 Hz, C*H*$_a$H$_b$COCH$_3$), 3.03 (dddd, 1 H, *J* = 11.7, 8.6, 8.6, 3.9 Hz, C*H*CO$_2$),

2.64 (dd, J = 18.0, 8.3 Hz, $CH_aH_bCOCH_3$), 2.59 (ddd, J = 11.7, 8.6, 5.9 Hz, $CH_\alpha CH_\beta CHCO_2$), 2.20 (s, 3 H, $COCH_3$), 1.77 (m, 1 H, $CH_2CH_aCH_bCHOCO$), 1.62 (m, 1 H, $CH_2CH_aCH_bCHOCO$), 1.50 (ddd, 1 H, J = 11.7, 11.7, 9.8 Hz, $CH_\alpha CH_\beta CHCO_2$), 1.45 (m, 1 H, $CH_3CH_2CH_aCH_b$), 1.36 (m, 3 H, $CH_3CH_2CH_aCH_b$), 0.91 (t, 3 H, J = 6.8 Hz, CH_3); ^{13}C NMR (125 MHz) δ 205.59, 178.27, 79.25, 43.52, 36.53, 35.27, 34.88, 29.84, 27.16, 22.26, 13.76; IR (neat) 2956, 2933, 2870, 1773, 1718, 1456, 1411, 1370, 1356, 1322, 1284, 1259, 1210, 1183, 1126, 1007, 971 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.77; H, 8.98.

(±)-*trans*-2-(2-Oxopropyl)-γ-octanoic Lactone (4t). By a procedure similar to that used for the preparation of **4c**, alkene **6t** (1.65 mmol) was oxidized to ketone **4t** in 80% yield: ^1H NMR (500 MHz, $CDCl_3$) δ 4.55 (dddd, 1 H, J = 8.8, 8.1, 5.8, 3.9 Hz, $CHOCO$), 3.03 (dd, 1 H, J = 19.0, 3.9 Hz, $CH_aH_bCOCH_3$), 3.02 (dddd, 1 H, J = 9.8, 9.3, 8.8, 3.4 Hz, $CHCO_2$), 2.69 (dd, J = 19.0, 9.3 Hz, $CH_aH_bCOCH_3$), 2.23 (ddd, 1 H, J = 13.7, 9.8, 3.9 Hz, $CH_\alpha CH_\beta CHCO_2$), 2.01 (ddd, J = 13.7, 8.8, 8.8 Hz, $CH_\alpha CH_\beta CHCO_2$), 2.20 (s, 3 H, $COCH_3$), 1.71 (m, 1 H, $CH_2CH_aCH_bCHOCO$), 1.58 (m, 1 H, $CH_2CH_aCH_bCHOCO$), 1.43 (m, 1 H, $CH_3CH_2CH_aCH_b$), 1.36 (m, 3 H, $CH_3CH_2CH_aCH_b$), 0.91 (t, 3 H, J = 6.8 Hz, CH_3); ^{13}C NMR (125 MHz) δ 205.55, 178.82, 78.86, 44.05, 35.02, 34.33, 33.07, 29.83, 27.29, 22.27, 13.82; IR (neat) 2957, 2934, 2862, 1766, 1718, 1458, 1356, 1161, 1007 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.86; H, 9.15.

Acknowledgment. This investigation was supported by grant GM-34492 awarded by the DHHS. We thank Professor Albert T. Sneden who kindly provided the sample of rollinone for which data are here reported, Professor J. McLaughlin for providing unpublished NMR data for compound **2b**, Dr. Vikram Roongta of the University of Minnesota for his considerable help with NOE and COSY studies, and the 3M Company for a graduate fellowship (P.R.H.).

Synthesis of the First Branched Quaterthienyls

Daniel M. Perrine,* David M. Bush, and Eugene P. Kornak

Department of Chemistry, Loyola College in Maryland, 4501 North Charles Street, Baltimore, Maryland 21210-2699

Ming Zhang,† Young H. Cho, and Jacques Kagan

Department of Chemistry, University of Illinois at Chicago, P.O. Box 4348, Chicago, Illinois 60680

Received March 19, 1991

The first synthesis of four of the 16 possible isomeric branched quaterthienyls (thienylterthiophenes) is reported. Thus, 5′-(2-thienyl)-2,2′:3′,2″-terthiophene, 5′-(2-thienyl)-2,2′:3′,3″-terthiophene, 5′-(3-thienyl)-2,2′:4′,2″-terthiophene, and 5′-(3-thienyl)-2,2′:4′,3″-terthiophene, **2a–5a**, were synthesized from the respective trithienyl-1,4-butanediones **10–13**, which were obtained in good yield via the Stetter reaction. The structures of **2a–5a** were supported by 2D COSY spectra.

In 1945, Zechmeister[1] et al. reported that α-terthienyl (2,2′:5′,2″-terthiophene, α-T, 1; Chart I), synthesized four years previously by Steinkopf,[2] was a natural component of marigolds (*Tagetes erecta*, L). In 1958, Uhlenbroek and Bijloo[3] discovered that 1 was a powerful nematocide, and in 1972, Gommers[4] observed that it was phototoxic. Numerous studies since then have shown that 1, which acts as a singlet-oxygen sensitizer, is one of the most phototoxic compounds known.[5] The isomers of α-T and its higher oligomers are also of growing interest as repeating units for the construction of electrically conductive polymers.[6] Recently, transition-metal-catalyzed aryl cross-coupling reactions have been used to synthesize all 14 possible isomeric terthiophenes.[7] These and numerous other structural modifications of 1 have been tested for phototoxicity,[8] but most (as well as Steinkopf's α,α,α-quaterthienyl, see below) are less phototoxic; additionally, there is—as with 1 itself—little or no species or target-cell specificity.

There are, on the other hand, 94 possible isomeric "quaterthienyls" (by which we mean any 4-thiophene-ring oligomer). The structure of 78 of these, by analogy to the alkanes, can be described as linear, having no ring attached to more than two others (these are quaterthiophenes by IUPAC nomenclature); the remaining 16 are branched and have a central ring attached to three others (IUPAC thienylterthiophenes).[9] Only two quaterthienyls have been synthesized to date, both linear: in 1937, Steinkopf[10a] reported a very poor yield, by Ullmann coupling, of 2,2′:5′,2″:5″,2‴-quaterthiophene, which he called "α,α,α-

† Author to whom inquiries concerning NMR spectra should be addressed.

(1) (a) Zechmeister, L.; Sandoval, A. *Arch. Bio.* **1945**, *8*, 425–430. (b) Sease, J. W.; Zechmeister, L. *J. Am. Chem. Soc.* **1947**, *69*, 270–273. (c) Sease, J. W.; Zechmeister, L. *J. Am. Chem. Soc.* **1947**, *69*, 273–275. For leading references to the isolation of α-terthienyl from numerous related species, see: (d) Bohlmann, F.; Zdero, C. In *Thiophene and Its Derivatives*; Gronowitz, S., Ed. (Vol. 44 of *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.); John Wiley: New York, 1985; Part 1, pp 261–323. (e) Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973.

(2) Steinkopf, W.; Leitsmann, R.; Hofmann, K. H. *Liebigs Ann. Chem.* **1941**, *546*, 180–199.

(3) Uhlenbroek, J. H.; Bijloo, J. D. *Recl. Trav. Chim. Pays-Bas* **1958**, *77*, 1004–1009; **1959**, *78*, 382–390.

(4) (a) Gommers, F. J. *Nematologica* **1972**, *18*, 458–462. (b) Gommers, F. J.; Geerlings, J. W. G. *Nematologica*, **1973**, *19*, 389–393.

(5) For a recent review of the literature concerning bi- and trithiophenes, see: (a) Kagan, J. *Progr. Chem. Org. Nat. Prod.* **1991**, *56*, 87–169. See also: (b) *Light-Activated Pesticides*; Heitz, J. R., Downum, K. R., Eds.; ACS Symposium Series 339; American Chemical Society: Washington, DC, 1987.

(6) (a) Tour, J. M.; Wu, R.; Schumm, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 5662–5663. (b) Ferraris, J. P.; Skiles, G. D. *Polymer* **1987**, *28*, 179–182. (c) Frommer, J. E.; Chance, R. R. *Encyclopedia of Polymer Science and Engineering*; Mark, H. F., Bikales, N. M., Overberger, C. G., Menges, G., Kroschwitz, J. I., Eds.; Wiley: New York, 1986; Vol. 5, pp 462–507 and references cited therein.

(7) (a) Jayasuriya, N.; Kagan, J. *Heterocycles* **1986**, *24*, 2901–2904. (b) Jayasuriya, N.; Kagan, J. *Heterocycles* **1986**, *24*, 2261–2264. (c) Carpita, A.; Rossi, R. *Gazz. Chim. Ital.* **1985**, *115*, 575–583. For a review, see: (d) Rossi, R. *Bioact. Mol.* **1988**, *7*, 29–45.

(8) For leading references, see: (a) Arnason, J. T.; Philogene, B. J. R.; Berg, C.; MacEachern, A.; Kaminski, J.; Leitch, L. C.; Morand, P.; Lam, J. *Phytochemistry* **1986**, *25*, 1609–1611. (b) Kagan, J.; Kagan, P. A.; Buhse, H. E., Jr. *J. Chem. Ecol.* **1984**, *10*, 1115–1122. (c) Downum, K. R.; Hancock, R. E. W.; Towers, G. H. N. *Photobiochem. Photobiophys.* **1983**, *6*, 145–152.

0022-3263/91/1956-5095$02.50/0