mixture was shaken in a separatory funnel with water (40 mL) containing $NaHCO_3$ (1.4 g, 16.7 mmol). When the initial gas evolution had ceased, the two-phase system was left for 3 days to complete the elimination. Flash chromatography (SiO_2/CH_2Cl_2:hexane = 1:1) and Kugelrohr distillation afforded 0.31 g (89%) of compound **20a** as an isomeric mixture (*E*:*Z* = 4:1). The *Z* isomer was separated by using HPLC (Waters M-45 instrument; μ-Porasil column; EtOAc:hexane = 1:99) from the well-characterized[38] *E* isomer. *Z* isomer: ^1H NMR (400 MHz) δ 0.89 (t, 3 H), 1.29–1.39 (several peaks, 6 H), 2.06 (s, 3 H), 2.09 (m, 2 H), 4.62 (d, 2 H), 5.54 (m, 1 H), 5.64 (m, 1 H); J_{H-H} olefinic = 10.9 Hz.

Compounds **19**[39] and **20b**[39] were similarly prepared. For the preparation of compounds **13**, **20c**, and **20d**, the two-phase system was left for 24 h, 24 h, and 4 days, respectively, to complete the elimination. ^1H NMR and/or analytical data for new compounds prepared according to method C are as follows. For yields and *E*:*Z* ratios, see Table II.

13: δ 2.33 (s, 3 H), 4.96 (d, 2 H), 6.11 (t, 1 H), 7.34–7.57 (several peaks, 8 H), 8.06 (m, 2 H); mp 57–8 °C. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.98; H, 5.57.

20c. The *Z* isomer was previously described.[40] *E* isomer: ^1H NMR (selected peaks) δ 2.08 (s, 3 H), 4.61 (d, 2 H), 4.84 (d, 2 H).

In the preparation of compound **20d** according to method C, the selenide mixture **5d** + **6d** was isolated in 58% yield.

Compounds **22** and **24** were dissolved in CH_2Cl_2 and treated with aqueous $NaHCO_3$ as described in method C (elimination time 21 and 5 days, respectively) to give compounds **23** and **25** in 96 and 98% yields, respectively.

23: ^{13}C NMR (400 MHz) δ 14.08, 21.18, 27.27, 37.10, 42.21, 60.74, 60.97, 65.99, 126.97, 128.99, 170.30, 170.80, 172.72; ^1H NMR (400 MHz) δ 1.24 (t, 3 H), 1.25 (t, 3 H), 2.04 (s, 3 H), 2.24 (ddd, 1 H, J = 2.4, 3.5, and 14.7 Hz), 2.35 (ddd, 1 H, J = 4.4, 11.8, and 14.7 Hz), 2.97 (ddd, 1 H, J = 3.5, 5.1, and 11.8 Hz), 3.60 (dd, 1 H, J = 5.1 and 5.1 Hz), 4.11–4.20 (several peaks, 4 H), 5.31 (m, 1 H), 5.95 (dd, 1 H, J = 4.6 and 9.8 Hz), 6.10 (dd, 1 H, J = 5.1 and 9.8 Hz). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.09. Found: C, 58.74; H, 7.21.

25: ^{13}C NMR (400 MHz) δ 14.09, 21.18, 30.26, 37.42, 44.02, 60.92, 61.22, 64.78, 125.65, 129.43, 170.38, 171.78, 174.09; ^1H NMR (400 MHz) δ 1.27 (t, 3 H), 1.28 (t, 3 H), 1.86 (ddd, 1 H, J = 4.3, 12.7, and 14.2 Hz), 2.07 (s, 3 H), 2.20 (ddd, 1 H, J = 3.0, 3.0, and 14.2 Hz), 3.10 (ddd, 1 H, J = 3.0, 10.1, and 12.6 Hz), 3.50 (dd, 1 H, J = 1.5 and 10.1 Hz), 4.14–4.23 (several peaks, 4 H), 5.25 (m, 1 H), 5.91 (dd, 1 H, J = 4.8 and 10.0 Hz), 6.07 (dd, 1 H, J = 1.5 and 10.0 Hz). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.09. Found: C, 59.12; H, 7.15.

***trans*-1-Acetoxy-2-chloroacenaphthene (15).** To a stirred solution of selenide **14** (1.13 g, 3.1 mmol) in $CHCl_3$ (10 mL) at ambient temperature was added SO_2Cl_2 (0.42 g, 3.1 mmol). The orange-red solution was then left for 4 days. Evaporation and flash chromatography (SiO_2; CH_2Cl_2:hexane = 1:1) of the residue afforded 0.59 g (78%) of compound **15**, mp 99 °C (lit.[41] mp 94–5 °C).

2-Bromooctyl phenyl selenide was prepared by treatment of PhSeBr (0.54 g, 2.2 mmol) with 1-octene (0.25 g, 2.2 mmol) in $CHCl_3$ (2 mL) for 24 h by analogy with a literature procedure.[10] The reaction mixture was then poured into 5 mL of the acetate buffer solution used in the typical acetoxyselenenylation procedure (vide supra). Workup afforded a 48:52 mixture of compounds **5a** and **6a** (yield not determined).

Acknowledgment. Financial support by the Swedish Natural Science Research Council and Carl Tryggers Stiftelse is gratefully acknowledged.

Registry No. **1a**, 51558-95-3; **1b**, 63603-28-1; **1c**, 67007-25-4; **2a**, 118270-70-5; **2b**, 116117-96-5; **2c**, 118270-69-2; **5a**, 67007-28-7; **5a** (olefin), 111-66-0; **5b**, 118270-52-3; **5b** (olefin), 112-41-4; **5c**, 118270-54-5; **5c** (olefin), 300-57-2; **5d**, 118270-56-7; **5d** (olefin), 591-87-7; **5e**, 118270-57-8; **5e** (olefin), 583-04-0; **5f**, 118270-59-0; **5f** (olefin), 1746-13-0; **5g**, 118270-61-4; **5g** (olefin), 18203-32-2; **6a**, 67007-29-8; **6b**, 118270-53-4; **6c**, 118270-55-6; **6d**, 99018-35-6; **6e**, 118270-58-9; **6f**, 118270-60-3; **6g**, 118270-62-5; **7**, 118270-63-6; **7** (olefin), 766-90-5; **8**, 118270-64-7; **8** (olefin), 873-66-5; **9**, 118270-65-8; **9** (olefin), 5320-75-2; **10a**, 118270-66-9; **10a** (olefin), 14447-34-8; **10b**, 118270-71-6; **11a**, 26735-84-2; **11b**, 118270-77-2; **11c**, 25522-54-7; **11d**, 97146-99-1; **11e**, 118270-80-7; **11f**, 118270-78-3; **12**, 118270-79-4; **13**, 118270-81-8; **14**, 118270-67-0; **14** (olefin), 208-96-8; **15**, 50499-75-7; **16**, 33033-36-2; **17**, 118270-68-1; **17** (olefin), 645-49-8; (*E*)-**18**, 24647-07-2; (*Z*)-**18**, 13892-81-4; **19**, 7217-71-2; (*E*)-**20a**, 3913-80-2; (*Z*)-**20a**, 26806-12-2; (*E*)-**20b**, 21040-45-9; (*E*)-**20c**, 118270-82-9; (*Z*)-**20c**, 118270-83-0; (*E*)-**20d**, 31447-25-3; (*Z*)-**20d**, 31447-24-2; **22**, 118270-73-8; **22** (selenide), 118270-72-7; **23**, 118270-84-1; **24**, 118374-49-5; **24** (selenide), 118374-48-4; **25**, 118270-85-2; styrene, 100-42-5; [1-acetoxy-3-(benzoyloxy)-1-phenyl-2-propyl]phenylselenium dichloride, 118270-74-9; (2-acetoxy-3-phenylpropyl)phenylselenium dichloride, 118270-75-0; (2,3-diacetoxypropyl)phenylseleniumdichloride, 118270-76-1; acetophenone, 98-86-2; phenacyl phenyl selenide, 35050-01-2; 2-bromooctyl phenyl selenide, 66221-85-0; α-acetoxystyrene, 2206-94-2.

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4-(Phenylsulfonyl)butanoic Acid. Preparation, Dianion Generation, and Application to Four-Carbon Chain Extension[1]

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Received September 6, 1988

The bishomoenolate dianion of 4-(phenylsulfonyl)butanoic acid was investigated. It was observed that the dianion could be generated in greater than 95% yield with 200 mol % of *n*-BuLi at certain concentrations. The dianion was reacted with a variety of aldehydes to afford, after cyclization, substituted tetrahydropyran-2-ones (lactones). These derivatives were reductively eliminated to afford methyl 4-butenoates in yields of 56–85%.

Carboxylic acid dianions have emerged as valuable tools in carbon–carbon bond formation.[2] This is due, in part, to their ready availability and reluctance to self condense. As a result, they are frequently desirable reagents or

0022-3263/89/1954-0890$01.50/0

coupling partners. For example, acetic acid[3] and congener[2e,f,i] dianions have been used. Other select studies include stereoselective addition to carboxylic acid dianions,[4] oxidative coupling,[5] and α,β-unsaturated acid dianions.[6]

Recently, we reported[7] our initial contribution to the arena of carboxylic acid dianions with the introduction of "remote" carboxylic acid dianions, where the anion sites are insulated by intervening methylene units. Specifically, the dianion of 4-(phenylsulfonyl)butanoic acid (4-PSBA) (1) was investigated. This minor modification of carboxylate dianion methodology has witnessed meager exploration[8] despite obvious implications to organic synthesis.

Homologations of aldehydes and ketones have been reviewed.[9] While there are a plethora of one- and two-carbon homologations, fewer three-carbon methods exist. And naturally, extant four-carbon homologation methods are limited. Some seldom-employed four-carbon chain extensions include the Wittig,[10] vinylogous Reformatsky,[11] and others.[12] The vinylogues of masked ester enolates have been employed, but their ambident nature (α vs γ attack) must be recognized and the regioselectivity controlled. The production of α,β-unsaturated carbonyls by

Scheme I

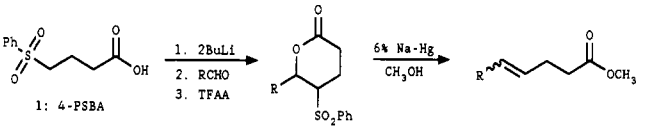
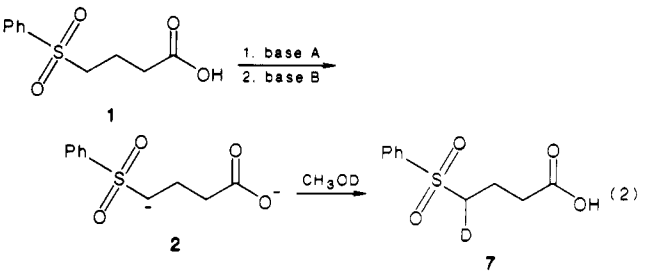


Table I

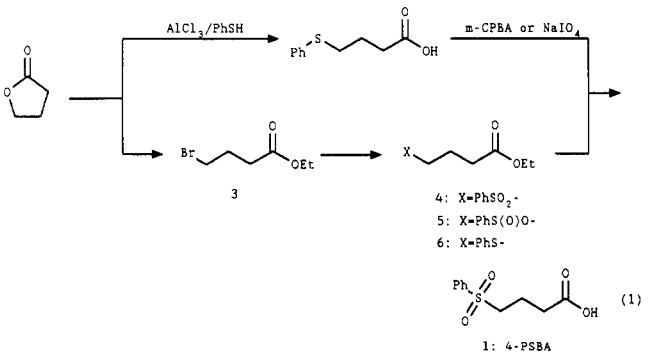


base A	base B	% D
LDA	LDA	71
NaH	LDA	55
KH	LDA	60
NaH	BuLi	70
KH	BuLi	72
BuLi	BuLi	>96

many of these methods[9,11,12] should be noted with respect to the scant number of γ,δ-unsaturated carbonyls prepared. Overall, far less investigation has been conducted to develop four-carbon homologation reagents, and few methods are capable of regio- and stereocontrol of the olefin while maintaining the oxidation state of the appended carbon. Therefore, we sought to extend the utility of 1 to the application of four-carbon chain extensions (Scheme I) and began to address the question of stereo- and regiocontrol of the olefin. Herein, we report the outcome of this study and some structural details of the intermediates.

Results and Discussion

Preparation and Bisdeprotonation of 4-(Phenylsulfonyl)butanoic Acid. Despite the structural simplicity of 1, there are scant reports of its use or preparation.[13] Thus, we sought to devise an inexpensive pathway that would also be amenable to scale up (i.e. >250 g). We first prepared 1 via Lewis acid promoted ring opening of butyrolactone[14] by thiophenol and subsequent oxidation with either *m*-CPBA or sodium periodate (eq 1). Although



successful (52% overall yield), the equimolar use of aluminum chloride and thiophenol deterred our interest to-

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ward large-scale preparation. Likewise, thiophenol alkylation with ethyl 4-bromobutyrate[15] (3) to ethyl 4-(phenylthio)butyrate (6), subsequent oxidation, and saponification succeeded but was not desirable for similar reasons. The use of benzenesulfinic acid (sodium salt) was then attempted to circumvent both thiophenol alkylation and oxidation steps. Unfortunately, reactions of sulfinates are known to yield mixtures of S- and O-alkylation products.[16] This minor problem surfaced but was resolved.

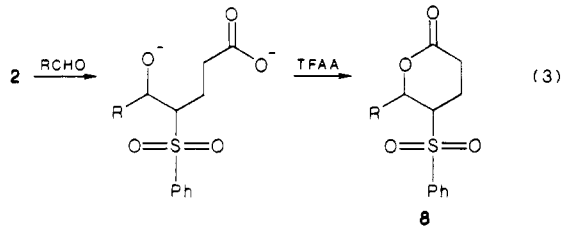
In a routine procedure, ethyl 4-bromobutyrate[15] (3) was converted to the iodide in 96% yield.[17] The crude ethyl 4-iodobutyrate was reacted with 110 mol % of benzenesulfinic acid sodium salt in ethanol to afford greater than 90% of an 8:1 mixture of S- and O-alkylated products (4, 5) by NMR spectroscopy and isolation. The isomer mixture was directly saponified to the butanoic acids, which, after acidification and extraction into diethyl ether, deposited needles of pure 1 upon standing, the sulfinate isomer remaining in solution. The three-step procedure affords a 60% overall yield of 1 without any intermediate purification. 4-(Phenylsulfonyl)butanoic acid may be stored for prolonged periods at room temperature with little decomposition.

Generation of dianion 2 in high conversion was not straightforward. Iwai[8d] reported 70% conversion of 3-(phenylsulfonyl)proprionic acid to the homoenolate dianion with 200 mol % of lithium diisopropylamide (LDA). Likewise, only 71% deuterium incorporation was observed with 1 by treatment with 200–250 mol % LDA (eq 2). Further, base combinations of differing cations (Table I) and/or HMPA, TMEDA additives had a negligible effect. The use of 200 mol % *n*-butyllithium (*n*-BuLi) resulted in greater than 96% deuterium incorporation at C-4 by NMR analysis. Exclusive exchange at C-4 is noteworthy. Precipitation of the dianion was observed with concentrations greater than 0.05 M with 1.6 M *n*-BuLi presumably due to the hexane content. The use of 2.5 M *n*-BuLi is suggested, allowing higher concentration of dianion to be achieved. Interestingly, the golden yellow dianion solution is preceded by initial precipitation of the carboxylate salt. This observation may be suggestive of dianion dipole stabilization.[7,18]

Preparation of Tetrahydropyran-2-ones (Lactones). The addition of sulfone-stabilized anions to carbonyls is well documented.[19] Owing to the size of the phenylsulfone group, however, additions may be sluggish (although not generally exhibited with aldehydes) and further may be complicated by reversible reaction. In the case of 2, little addition problem was observed at temperatures ranging from −78 °C to room temperature. In addition, the generated dianion survives room temperature for prolonged periods without sacrificing yields dramatically. For example, only a 5% decrease in yield was observed with addition to benzaldehyde after the dianion was stirred at room temperature for 4 h.

The preparation of some of the tetrahydropyran-2-ones has been reported.[7] This study was limited to aldehyde additions. In general, the aldehyde (4 mmol; neat or THF solution) was added to 4.25 mmol of dianion 2 in 50 mL of tetrahydrofuran at −78 °C and stirred for 0.5 h. Trifluoroacetic anhydride[20] (TFAA; 8 mmol) was added, and the reaction mixture was stirred for an additional 0.5 h while being brought to room temperature. After standard workup, the crystalline products **8a–f** (eq 3)[21] were obtained in greater than 90% yield. Column purification afforded isolated yields from 65 to 85%. In some cases, crude products were used directly in the subsequent transformation or crystallized from chloroform–ether mixtures. The results are summarized in Table II. A nice feature of this procedure is that all reagents are removed in the bicarbonate extraction.

Table II. Preparation of 3,4,5,6-Tetrahydropyran-2-ones



(3)

entry	R	% yield[a]	MP, °C[b]	J_{H3-H4}, Hz
8a	*n*-C_3H_7	77	101	10.8
8b	CH_3CH=CH	75	95–6	6.2
8c	Ph	84	114–5	6.1
8d	PhCH=CH	72	128–9	6.5
8e	*n*-C_7H_{15}	65	100–2	10.7
8f	*tert*-C_4H_9	85	231	2.6

[a] After chromatography. [b] Single diastereomer.

The addition–cyclization sequence includes regiochemical 1,2-addition **8b,d** and versatility with respect to reactivity of both aryl and alkyl aldehydes. Branching at the α-position of **8f** did not adversely affect the reaction.

Tetrahydropyran-2-one Stereochemistry. Of particular interest to this investigation was the stereochemical outcome of the 6-substituted 5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-ones (**8a–f**). As expected, the orientation of the substituents was found to be predominantly trans on the basis of NMR analysis (Table II). The H-C3/H-C4 coupling constant is dependent upon both phenylsulfonyl group orientation (i.e. Karplus angle) and the slight ring flattening imparted by the lactone function.[22] A discussion of the former point is warranted.

For specific analysis, the 6-phenyl-5-(phenylsulfonyl)-(2*H*)-tetrahydropyran-2-one (**8c**) was examined in detail, owing to its readily assignable NMR spectrum and chromatographic characteristics. Chromatographic isolation of a 4-mmol reaction afforded a 94:6 trans/cis ratio by weight as assigned by NMR (J_{trans} = 6.1 Hz; J_{cis} = 3.78 Hz). Noticeably, the coupling constants did not correlate well with the Karplus dihedral angle[23] where the trans coupling constant would be expected to be somewhat larger. It is

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(22) Conformation of oxacyclohexane ring described as flattened chair, see: (a) Lambert, J. B. *Acc. Chem. Res.* **1971**, *4*, 87. Related studies, see: (b) Rao, V. M.; Kewly, R. *Can. J. Chem.* **1969**, *47*, 1289. (c) Spragg, R. A. *J. Chem. Soc. B* **1968**, 1128. (d) Harris, R. K.; Spragg, R. A. *J. Chem. Soc. B* **1968**, 684. (e) Smith, W. B.; Shoulders, B. A. *J. Phys. Chem.* **1965**, *69*, 579. Heterocyclohexane conformation, see: (f) Riddell, F. G. *Quart. Rev.* **1967**, *21*, 364. (g) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1. (h) Eliel, E. L. *Pure Appl. Chem.* **1971**, *25*, 509.
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known, however, that electronegative substituents on the H–C–C–H unit result in a shift in the Karplus curve to the right.[24] In consort with this fact and in an effort to determine these angles more precisely, MM2 calculations were conducted. Minimized conformations suggest that the vicinal hydrogen dihedral angle (H–C_3–C_4–H) for the trans and cis isomers are 176.66° and 51.54°, respectively. The phenyl rings adopted a periplanar arrangement when minimized for the trans orientation, which should be noted and possibly accounts for the large angle deviation from NMR analysis. The calculations further imply a small degree of buttressing between vicinal substituents in the cis case. Support for this assignment is also apparent in the chemical shift of these isomers as the axial proton (trans relationship) resonates at higher field than the corresponding equatorial proton (compare **8c**: δ_{cis} = 5.95 and δ_{trans} = 5.77). All nonbranching derivatives in this study were found to have similar bond angle values when minimized. It should be noted that there are obvious limitations in interpretation when extending the molecular mechanics analyses to solution characteristics.

When the R group was *tert*-butyl **8f**, a 2.7-Hz coupling constant was observed. Thus, a pronounced effect on the Karplus angle is expected, indicating ring perturbation of the trans isomer or alternatively, a predominant cis isomer where the phenylsulfonyl group has adopted the axial position. In this regard, a partial explanation may be that the electronegative group (i.e. $PhSO_2$) is rigidly antiperiplanar with respect to the affected proton, thus reducing the coupling constant.

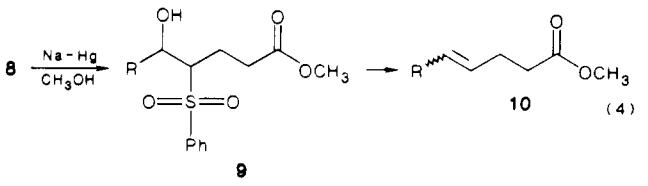
The conformational perturbation of vicinally positioned sterically demanding cis groups has been examined[25] where the crowding regulates ring shape. If the trans orientation of **8f** exists, calculations suggest an H–C_3–C_4–H dihedral angle of 132°, which virtually eclipses the C-3, C-4 substituents and respective vicinal H-4, H-3 protons to avoid crowding. Nuclear Overhauser studies were inconclusive. Overall, in the case of **8f**, either the phenylsulfonyl group has truly adopted the axial position or the vicinal groups have buttressed themselves into a flattened orientation where the vicinal bond angle is 132° as calculations suggest. This latter situation would more closely resemble *cis*-1,2-di-*tert*-butylcyclohexane, which assumes a twist-boat conformation.

Conversion of Tetrahydropyran-2-ones to Methyl 4-Butenoates. The Julia–Lythgoe coupling sequence involves the reaction of β-acyloxy sulfones with Na–Hg amalgam to afford olefins.[26] The method of Trost[27] has been instrumental in effecting this reductive-elimination transformation where sodium hydrogen phosphate is added to scavenge base (CH_3O^-) as large amounts of methoxide are produced during the transformation, which can be problematic to base sensitive groups. To our advantage, we have prepared an intramolecular version of the β-acyloxy sulfone (**8a–f**) with the expectation that the methoxide produced would induce lactone ring opening and ester formation with concomitant β-elimination, affording the regiochemically pure butenoate. When the tetrahydropyran-2-ones (**8a-f**) were treated with 6% Na–Hg amalgam in methanol (0 °C to room temperature), good yields of methyl-4-butenoates **10** were achieved (Table III), presumably via a hydroxy sulfone intermediate **9** (vide infra). The two-step sequence constitutes an overall regiochemically directed conversion of aldehyde to methyl 4-butenoate or four carbon chain extension. Mention should be made of the fact that the chain-extended aldehydes prepared in this study were all somewhat volatile, and yields were effected accordingly. In cases where the substrate was of higher molecular weight, improved yields are obtained.[28]

The stereochemistry of the resulting olefin was found to be consistent with geometry and branching dependence reported by Lythgoe and co-workers (Table III),[26a,b,c] particularly noting the 80:20 *E*/*Z* mixtures for unbranched chains and the 97:3 *E*/*Z* ratio for the *tert*-butyl derivative. These values roughly support the radical intermediate mechanism proposed by Lythgoe.[26a]

The mechanism of the tethered ring opening–reductive elimination sequence was examined owing to possible stereochemical consequences. It was suspected that ring opening precedes elimination as evidenced by isolation of intermediate hydroxy sulfone **9** in small quantities. This aspect, unfortunately, would work against any possible

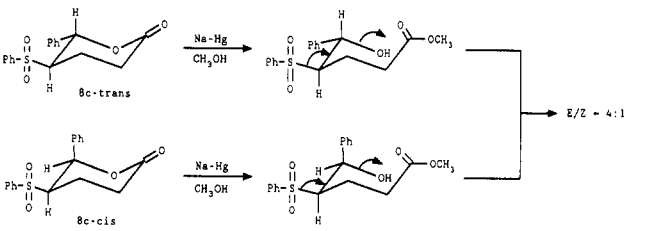
Table III. Conversion of 3,4,5,6-Tetrahydropyran-2-ones to Methyl 4-Butenoates



entry	R	yield of 10, %	*E*/*Z*[a]
10a	n-C_3H_7	80	4:1
10b	CH_3CH=CH	85	4:1
10c	Ph	70	4:1
10d	PhCH=CH	56	4:1
10e	n-C_7H_{15}	83	4:1
10f	*tert*-C_4H_9	81	97:3

[a] *E*/*Z* ratios were determined by GC and/or NMR analyses.

Scheme II



(24) For example, the axial–axial coupling constant with electron-withdrawing substituents present (in consort with an oxygen in the ring) is greatly lowered. See: (a) Lemieux, R. U.; Howard, J. *Can. J. Chem.* **1963**, *41*, 308. (b) Gunther, H. *NMR Spectroscopy*; John Wiley & Sons: New York, 1980.

(25) A large substituent may be forced into the axial position (higher energy) of a twist form as in the case of *cis*-1,2-di-*tert*-butylcyclohexane. See: Kessler, H.; Gusowski, V.; Hanack, M. *Tetrahedron Lett.* **1968**, 4665.

(26) The mechanism of the reductive elimination has been proposed as proceeding through a radical intermediate. A further one-electron reduction affords an anion, which is presumably responsible for the elimination. At either the radical or anion stage, free rotation about the participating carbons results in a mixture of rotomers of which the more favorable anti orientation is favored by approximately –0.8 kcal/mol. For further information, see: (a) Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97 and references therein. (b) Kocienski, P.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045. (c) Kocienski, P.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (d) Julia, M.; Paris, M.-J. *Tetrahedron Lett.* **1973**, 4833. For recent examples of the Julia–Lythgoe coupling sequence, see: (e) Alvarez, E.; Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 119 and references therein. (f) Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840.

(27) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(28) Most of the methyl 4-butenoates prepared in this paper were volatile enough to be lost in rotary evaporation. In other studies directed toward pheromone synthesis, yields of the chain extension process (two steps) achieved greater than 80% yield.

stereochemical enhancement over acyclic systems due to ring-locked precursors. To further examine this suspicion, 6-phenyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (**8c**) (trans:cis = 94:6) was subjected to base-induced methanolysis (CH_3OH, room temperature, 2 h, 5 mol % NaH) and subsequently treated with Na–Hg amalgam, which resulted in an identical yield and isomer composition of methyl 4-butenoate products (as compared to the one-pot reaction). Therefore, elimination to 4-butenoic acid and concomitant esterification does not occur to any noticeable extent. Elimination of β-hydroxy sulfones is known, although they are reported to be less reactive than the corresponding acetates and benzoates.[26d,e] In this instance, however, the overall process was quite rapid, completing in 0.5 h. Further evidence for the methoxide ring opening preceding elimination is manifested in the stereochemical outcome of the olefin. The cis and trans isomers of the 6-phenyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (**8c**) were treated separately with the reductive elimination conditions discussed above. In both cases, an 80:20 *E*/*Z* mixture was obtained (Scheme II). If elimination preceded esterification the geometry about the olefin would be strictly related to the lactone substituent stereochemistry, although little is known concerning the isomerization of olefins in the presence of Na–Hg amalgam. To test this consideration, pure *E* olefin was dissolved in methanol to which Na–Hg amalgam was added. After stirring for twice the normal reaction time, no olefin isomerization was observed, which substantiates ring opening as the primary event.

Conclusions

The dianion of 4-(phenylsulfonyl)butanoic acid is an easily generated species, which can be applied to the four-carbon chain extension of aldehydes. A notable feature of this extension methodology is the exclusive production of γ,δ-unsaturated butenoates that previously were difficult to obtain.[12n] Therein, this methodology should effectively complement existing homologations. Currently, we are examining control of the olefin stereochemistry by suppressing initial methoxide ring opening. Ancillary studies include manipulations of the heterocycle to lead to versatile natural product building blocks.

As reported previously,[7] the dianion also reacts with ketones that may be chain extended with similar expectations of olefin geometry. 4-(Phenylsulfonyl)butanoic acid has recently been applied to the synthesis of a pheromone[29] and to the preparation of piperidones.[30]

Experimental Section

General Methods. Melting points were determined by using a Mel-Temp melting point apparatus and are uncorrected. Proton NMR spectra were taken in deuterated chloroform ($CDCl_3$) on either a Varian EM 360A or VXR 300-MHz instrument. Carbon NMR was conducted on the VXR 300 instrument, and peaks are relative to the deuterated chloroform triplet (δ = 77.06). Pertinent ^1H NMR data are tabulated in the following order: chemical shift (ppm in δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (*J* in hertz), and number of hydrogens. Infrared data (IR; $CDCl_3$) were obtained on a Perkin-Elmer Model 1310 instrument. Salient IR features are tabulated in decreasing wavenumber (cm^{-1}). Gas chromatography analyses were done on a Hewlett-Packard Model 5890 fitted with a megabore capillary column no. 1251012 from J&W Scientific. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL. Mass spectral analyses were conducted by the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln.

Analytical thin-layer chromatography (TLC) was conducted with aluminum-backed silica plates (E. Merck) in diethyl ether or diethyl ether–petroleum ether mixtures. Visualization was affected with an ultraviolet lamp and/or anisaldehyde stain (a 2% solution of *o*-anisaldehyde in 95:4:1 absolute ethanol–concentrated sulfuric–glacial acetic acid) with heating and/or iodine. Flash chromatography[31] was conducted with diethyl ether–petroleum ether mixtures.

All solvents were distilled prior to use by literature methods.[32] 4-(Phenylsulfonyl)butanoic acid was recrystallized from chloroform–diethyl ether. Air- or water-sensitive reactions were conducted under a positive argon atmosphere utilizing standard techniques.[33] All carbonyl compounds were distilled from calcium hydride. Ethyl 4-bromobutyrate was prepared by the method of Lavety and Proctor[15] or purchased from Aldrich. Sodium benzenesulfinate and *n*-butyllithium (1.6 and 2.5 M) were purchased from Aldrich. Sodium–mercury amalgam (6%) was prepared by the modified method of Tischler in Feiser and Fieser (Vol. 1).[34] The material thus obtained was pulverized in a mortar and pestle to a fine powder and stored at 10 °C.

4-(Phenylsulfonyl)butanoic Acid (1). Sodium iodide (40 g, 266.6 mmol) was added to 150 mL of dry acetone and brought to gentle reflux, effecting solution. To this stirred solution was added ethyl 4-bromobutyrate (39 g, 200 mmol) dropwise over 1 h. Reflux was continued for 4 h or until no further precipitation was observed.[17] The mixture was cooled, diluted with an equal volume of diethyl ether, filtered, and rotary evaporated to an oil. The oil was taken up in 250 mL of diethyl ether and washed twice with 100-mL portions of 2% NaOH, water, and brine and dried over sodium sulfate, yielding 46.2 g (95.5%) of crude ethyl 4-iodobutyrate, R_f = 0.8 (ethyl ether). If stored, this product must be protected from heat and light. This product was used directly in the next step without purification. ^1H NMR: δ 1.3 (t, *J* = 8, 3 H), 1.95–2.7 (m, 4 H), 3.3 (t, *J* = 6, 2 H), 4.15 (q, *J* = 8, 2 H).

Ethyl 4-iodobutyrate (17 g, 70 mmol) was dissolved in 100 mL of absolute ethanol. To this solution was added sodium benzenesulfinate (15.75 g, 96 mmol), and the heterogeneous mixture was refluxed for 6 h or until TLC indicated consumption of the starting material. The mixture was then taken up in 100 mL of water and extracted thrice with 100-mL portions of ether. The organic layers were combined and washed with 100-mL portions of 5% NaOH, water, and brine, dried over sodium sulfate, filtered, and evaporated in vacuo to afford 16.24 g (90.6%) of an 8:1 mixture of phenylsulfonyl (**4**) (R_f = 0.31) and phenylsulfinate (**5**) (R_f = 0.54; 100% ethyl ether) butyrate esters. This mixture was used without further purification. Isolated (sulfone) ^1H NMR: δ 1.25 (t, *J* = 6.5, 3 H), 1.8–2.65 (m, 4 H), 3.25 (dd, *J* = 6 and 8, 2 H), 4.13 (q, *J* = 6.5, 2 H), 7.45–8.15 (m, 5 H).

The butyrate ester mixture (**4** + **5**) (23.0 g, 90 mmol) was dissolved in 20 mL of 95% ethanol. To this solution was added lithium hydroxide (6.0 g, 250 mmol) predissolved in 120 mL of water. The cloudy solution was stirred for 2 h while being monitored (TLC) for loss of starting ester. The mixture was, at completion, extracted twice with 100-mL portions of ethyl ether. The aqueous layer was acidified to pH = 4 with concentrated phosphoric acid and extracted thrice with 100 mL of diethyl ether. The organic layers were combined, washed with water and brine, and dried, and the solvent was removed to afford 16.2 g of a crystalline mass. Alternatively, the ether solution of 4-PSBA may be allowed to stand uncovered, depositing needles. The solid was taken up in a minimum amount of chloroform, and an excess of diethyl ether added to the solution. Needles of 4-(phenyl-

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(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(32) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: New York, 1980.
(33) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; John Wiley and Sons; New York, 1975.
(34) Tischler, M. In Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol 1, p 1030. This procedure was modified to 6% sodium by weight with no additional precaution.

sulfonyl)butanoic acid formed within the hour. The product was filtered, washed with petroleum ether, and dried in vacuo to afford 14.38 g (70%), 60.5% overall, from ethyl 4-bromobutyrate, mp 94 °C. Large-scale preparation (500 g) affords 56% overall yield. ^{1}H NMR: δ 1.97 (m, 2 H), 2.47 (t, J = 7.1, 2 H), 3.17 (t, J = 7.6, 2 H), 7.5–7.65 (m, 3 H), 7.86 (t, 2 H), 10.6 (s, 1 H). ^{13}C NMR: δ 18.06, 31.97, 54.97, 127.95, 129.39, 133.94, 138.59, 177.74.

4-Deuterio-4-(phenylsulfonyl)butanoic Acid (7). 4-(Phenylsulfonyl)butanoic acid (0.228 g, 1 mmol) was dissolved in 25 mL of dry tetrahydrofuran (THF) and chilled to −78 °C. n-Butyllithium in hexane (1.55 M, 1.3 mL, 200 mol %) was added, generating a yellow-orange solution. The dianion was stirred for 0.5 h and methanol-d_1 (99.6% enriched, 41 μL, 100 mol %) was introduced, quenching the color. The solution was stripped of solvent, and the solid was partitioned between ethyl ether and 5% NaOH. The aqueous layer was separated, neutralized with phosphoric acid, and extracted thrice with chloroform. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and rotary evaporated to afford 0.219 g (95.6%) of greater than 90% C-4 enriched product by NMR. ^{1}H NMR: δ 1.97 (q, J = 7.3, 2 H), 2.49 (t, J = 7.1, 2 H), 3.16 (m, 1 H), 7.61 (m, 3 H), 7.88 (t, 2 H). ^{13}C NMR: δ 17.98, 31.97, 54.70 (t), 127.98, 129.39, 133.91, 138.65, 177.77. Anal. Calcd for $C_{10}H_{11}DO_4S$ (229.276 at D% = 90): C, 52.38; H, 5.67. Found: C, 52.27; H, 5.27.

General Procedure for the Preparation of Tetrahydropyran-2-ones (Lactones). 4-(Phenylsulfonyl)butanoic acid (0.969 g, 4.25 mmol) was dissolved in 75 mL of anhydrous THF and chilled to −78 °C. n-Butyllithium (2.5 M, 8.4 mmol, 3.36 mL) was added dropwise, and the mixture was stirred for 0.5 h. The carbonyl compound (4 mmol) was added either neat or in 3 mL of THF, the solution generally being quenched of color. The dry ice bath was removed, and the solution was stirred for 0.5 h, with the temperature achieving −20 °C. Trifluoroacetic anhydride (TFAA; 8 mmol, 1.68 g, 1.13 mL) was added, and the reaction was monitored by TLC (baseline UV activity before TFAA then migrates in 100% ethyl ether; see representative R_f values below), generally requiring 0.25–0.5 h to complete cyclization.

The solution was poured into 75 mL of saturated sodium carbonate and diluted with 50 mL of ethyl ether. The aqueous layer was washed twice with 50 mL of ethyl ether. The organic extracts were combined and washed successively with 50-mL portions of saturated sodium carbonate and brine, dried over sodium sulfate, and rotary evaporated to a foam. The crude product(s) (yield 85–95%) was crystallized directly from chloroform–ethyl ether or flash chromatographed with ethyl ether–petroleum ether mixtures.

6-n-Propyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (8a). Procedure yields 0.870 g (77%, mixture of isomers) after chromatography. Mp 101 °C. ^{1}H NMR: δ 0.86 and 0.93 (t, 3 H), 1.38–1.49 (m, 1 H), 1.50–1.91 (m, 3 H), 1.99–2.13 (m, 1 H), 2.29–2.58 (m, 2 H), 2.74 (m, 1 H), 3.56 (m, 1 H), 4.70 (br d, J = 10.8, 1 H), 7.57–7.91 (m, 5 H). IR ($CDCl_3$): 1730, 1215, 1081, 1040, 925 cm^{-1}. R_f = 0.6 (100% Et_2O). Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.42. Found: C, 59.65; H, 6.46.

6-Crotyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (8b). Procedure yields 0.841 g (75%, mixture of isomers) after chromatography. Mp 95–96 °C. ^{1}H NMR: δ 1.58 (d, J = 6.5, 3 H), 2.19–2.55 (m, 3 H), 2.73–2.83 (m, 1 H), 3.35 (q, J = 19.0 and 6.21, 1 H), 5.12 (t, 1 H), 5.23–5.31 (m, 1 H), 5.70–5.78 (m, 1 H), 7.26–7.89 (m, 5 H). ^{13}C NMR: δ 17.68, 18.72, 27.29, 61.13, 76.59, 126.86, 128.89, 129.46, 132.48, 134.40, 137.34, 169.65. IR ($CDCl_3$): 1745, 1309, 1215, 1150, 1085, 1018 cm^{-1}. R_f = 0.12 (100% Et_2O). Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 59.92; H, 5.75.

6-Phenyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (8c). Procedure yields 1.062 g (84%, mixture of isomers) after chromatography. Mp 114–115 °C. Trans isomer. ^{1}H NMR: δ 2.21–2.33 (m, 1 H), 2.44–2.65 (m, 2 H), 2.87–2.98 (m, 1 H), 3.73 (q, J = 12.7 and 6, 1 H), 5.77 (d, J = 6, 1 H), 7.11–7.74 (m, 10 H). ^{13}C NMR: δ 18.36, 27.21, 62.17, 78.07, 126.46, 128.50, 128.84, 129.05, 129.37, 134.16, 136.83, 137.22, 169.60. R_f = 0.16 (100% Et_2O). Cis isomer. ^{1}H NMR: δ 3.96 (br q, J = 10.0 and 3.78, 1 H), 5.95 (d, J = 3.78, 1 H). ^{13}C NMR: δ 19.48, 27.62, 61.47, 78.38, 126.55, 128.09, 128.32, 128.62, 129.04, 129.38, 133.53, 134.46, 138.87, 168.73. R_f = 0.12 (100% Et_2O). IR ($CDCl_3$): 1743, 1450, 1380, 1310, 1218, 1148 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10. Found: C, 64.20; H, 5.06.

6-Cinnamyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (8d). Procedure yields 0.985 g (72%, mixture of isomers) after chromatography. Mp 128–129 °C. ^{1}H NMR: δ 2.21–2.44 (m, 2 H), 2.54 (m, 1 H), 2.81 (m, 1 H), 3.53 (q, J = 12.3 and 5.9, 1 H), 5.35 (t, J = 6.5, 1 H), 6.00 (dd, J = 6.3, 1 H), 6.57 (d, J = 15.7, 1 H), 7.19–7.88 (m, 10 H). IR ($CDCl_3$): 1770, 1465, 1325, 1265, 1170 cm^{-1}. R_f = 0.2 (100% Et_2O). Anal. Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30. Found: C, 66.77; H, 5.36.

6-n-Heptyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (8e). Procedure yields 0.878 g (65%, mixture of isomers) after chromatography. Mp 100–102 °C. ^{1}H NMR: δ 0.88 (t, 3 H), 1.12–1.43 (m, 9 H), 1.58–1.64 (m, 2 H), 1.77–1.86 (m, 3 H), 2.00–2.17 (m, 2 H), 2.33–2.60 (m, 2 H), 2.71–2.80 (m, 1 H), 3.53–3.60 (m, 1 H), 4.7 (dt, J = 10.7, 1 H), 7.59–7.75 (m, 5 H). ^{13}C NMR: δ 13.31, 17.50, 18.81, 21.80, 24.05, 25.08, 26.28, 26.44, 28.14, 28.20, 28.28, 31.00, 59.14, 77.02, 127.64, 128.82, 133.65, 137.45, 168.52. IR ($CDCl_3$): 1735, 1305, 1210, 1150, 1080, 1040 cm^{-1}. R_f = 0.6 (100% Et_2O). Anal. Calcd for $C_{18}H_{26}O_4S$: C, 63.74; H, 7.74. Found: C, 63.74; H, 7.72.

6-*tert*-Butyl-5-(phenylsulfonyl)-3,4,5,6-tetrahydropyran-2-one (8f). Procedure yields 1.01 g (85%, mixture of isomers) after recrystallization. Mp 231 °C. ^{1}H NMR: δ 1.31 (s, 9 H), 1.99–2.17 (m, 2 H), 2.51–2.61 (m, 1 H), 2.74–2.86 (m, 1 H), 3.59–3.63 (m, 1 H), 4.30 (d, J = 2.55, 1 H), 7.57–7.92 (m, 5 H). ^{13}C NMR: δ 23.59, 25.73, 26.80, 35.08, 56.90, 88.07, 128.01, 129.58, 134.17, 139.09, 169.38. IR ($CDCl_3$): 1735, 1465, 1375, 1318, 1213, 1145 cm^{-1}. R_f = 0.08 (100% Et_2O). MS, m/z (M^+ − $tert$-C_4H_9) calcd 239.0383, obsd 239.0378.

General Procedure for the Preparation of Methyl 4-Butenoate Derivatives. The tetrahydropyran-2-one (1 mmol) was dissolved in 10 mL of anhydrous methanol and chilled to 0 °C, 1.5 g of finely crushed Na–Hg amalgam (6%) was added, after which the reaction was monitored by TLC for loss of starting material. The reaction mixture at completion was diluted with 15 mL of ethyl ether and filtered into a separatory funnel containing 30 mL of ethyl ether and 30 mL of water. The aqueous layer was extracted twice more with 25 mL of ethyl ether. The organic layers were combined, extracted with brine, dried over sodium sulfate, and carefully evaporated to afford the desired butenoate.[35]

4-Octenoic Acid Methyl Ester (10a).[35a] Procedure yields 0.125 g (80%, mixture of isomers). ^{1}H NMR: δ 0.90 (t, 3 H), 1.37 (q, 2 H), 1.90–2.06 (m, 2 H), 2.26–2.51 (m, 4 H), 3.66 (s, 3 H), 5.35–5.51 (m, 2 H). IR ($CDCl_3$): 1728, 1465, 1380, 1215 cm^{-1}.

4,6-Octadienoic Acid Methyl Ester (10b).[35b] Procedure yields 0.131 g (85%, mixture of isomers). ^{1}H NMR: δ 1.72 and 1.77 (d, J = 6.59, 3 H), 2.30–2.58 (m, 4 H), 3.66 (s, 3 H), 5.47–5.73 (m, 2 H), 5.94–6.08 (m, 2 H). IR ($CDCl_3$): 1730, 1439, 1380, 1215 cm^{-1}.

5-Phenyl-4-pentenoic Acid Methyl Ester (10c).[35c] Procedure yields 0.133 g (70%, mixture of isomers). ^{1}H NMR: δ 2.40–2.72 (m, 4 H), 3.67 and 3.69 (s, 3 H), 5.59–5.68 and 6.17–6.27 (m, 1 H), 6.42–6.50 (m, 1 H), 7.21–7.37 (m, 5 H). IR ($CDCl_3$): 1725, 1439, 1365, 1258, 1200 cm^{-1}.

7-Phenyl-4,6-heptadienoic Acid Methyl Ester (10d). Procedure yields 0.121 g (56%, mixture of isomers). ^{1}H NMR: δ 2.30–2.78 (m, 4 H), 3.68 and 3.69 (s, 3 H), 5.76–5.84 (m, 1 H), 6.19–6.29 (m, 1 H), 6.44–6.58 (m, 1 H), 7.18–7.46 (m, 5 H). ^{13}C NMR: δ 23.51, 28.05, 33.77, 51.55, 123.90, 126.21, 127.29, 128.54, 130.00, 131.03, 131.63, 132.75, 137.47, 173.29. IR ($CDCl_3$): 1725, 1438, 1365, 1258, 1200. MS, m/z (M^+) calcd 216.1150, obsd 216.1129.

4-Dodecenoic Acid Methyl Ester (10e).[35d] Procedure yields 0.164 g (83%, mixture of isomers). ^{1}H NMR: δ 0.90 (t, 3 H), 1.25 (s, 10 H), 1.92–2.16 (m, 4 H), 2.23–2.40 (m, 2 H), 3.66 (s, 3 H), 5.33–5.45 (m, 2 H). IR ($CDCl_3$): 1728, 1465, 1380, 1218 cm^{-1}.

6,6-Dimethyl-4-heptenoic Acid Methyl Ester (10f). Procedure yields 0.138 g (81%, mixture of isomers). ^{1}H NMR: δ 0.97 (s, 9 H), 2.23–2.50 (m, 4 H), 3.66 (s, 3 H), 5.29 (dt, J = 15.6, 1

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H), 5.48 (d, J = 15.6, 1 H). ^{13}C NMR: δ 28.02, 29.64, 32.73, 34.38, 51.32, 122.49, 142.83, 173.61. IR ($CDCl_3$): 1730, 1465, 1380, 1215 cm^{-1}. Anal. Cald for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.65; H, 10.84.

Calculations. All calculations were conducted on an IBM PC fitted with an 8087 math coprocessor utilizing "PCMODEL", a modified version of Prof. C. Still's (Columbia University) MODEL software program (VAX version 1.1) by Serena Software, Box 3076, Bloomington, IN, 47402-3076, 1987 Edition. MMX calculations for all pentanolides were based on at least 200 iterations to a minimized change of 0.02 kcal/mol. Bond angles were obtained from these minimized structures.[36]

Acknowledgment. We wish to acknowledge the kind financial support of NIEHS (Grant. No. ES04434-01) and Loyola University of Chicago for the purchase of the VXR-300 MHz NMR used in this study. We also wish to thank Prof. D. Crumrine (Loyola University) and Prof. Steven Ley (Imperial College, U.K.) for useful suggestions. We also wish to thank David Baehr for large-scale preparations of 4-PSBA and supporting data.

(36) We wish to thank the referee for recalculation (using PC Model Version 2) of some conformations.

Total Synthesis of (+)-Colletodiol: New Methodology for the Synthesis of Macrolactones[1]

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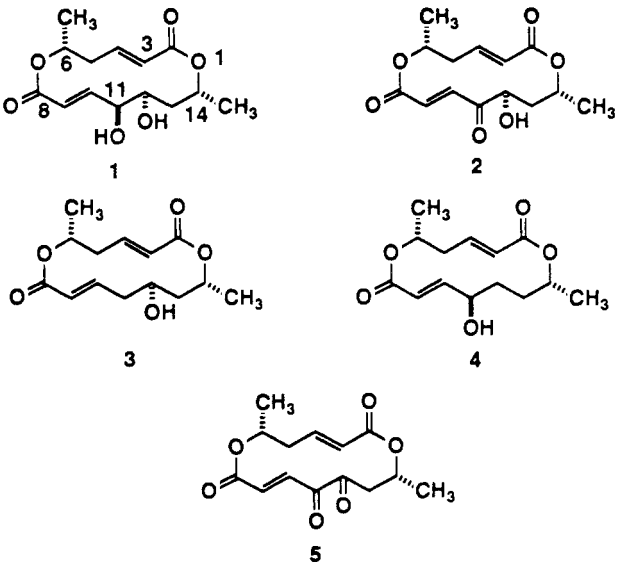
Received May 12, 1988

Synthetic efforts directed toward two different structures suggested for the macrocyclic bis(lactone) colletodiol are detailed. The initial approach to an incorrect structure (C_{11} epi) relies upon the manipulation of methyl α-D-glucopyranoside to set the required stereochemistry for the C_8–C_{14} segment of the C_{11} epi structure. The second approach, initiated after structural revision based upon X-ray crystallographic evidence, employs a Lewis acid mediated addition of allylstannane **33** to β-alkoxy aldehyde **34** to set the stereochemistry of the C_8–C_{14} subunit. This route, which employs a number of new synthetic reactions developed specifically for this problem, gives (+)-colletodiol in nine linear operations and 8.2% overall yield.

Colletodiol is a macrocyclic bis(lactone), which has been isolated as a metabolite of the fungi *Colletorichum capsici* by Grove[2] and from *Chaetomium funicola* by Powell;[3] the gross structure has been elucidated by both Powell[3] and McMillan.[4] McMillan has also reported on the absolute stereochemistry of colletodiol[5] (**1**) and three more cometabolites of *Colletotrichum capsici*: colletoketol (**2**), colletol (**3**), and colletoallol (**4**), although this assignment was later revised.

This class of compounds went largely unnoticed until 1980 when Ronald[6] reported the isolation and structure determination of grahamimycin A_1 (**5**) and also described significant antibacterial activity against a variety of pathogenic microorganisms.

In 1982, Seebach established the absolute configuration of grahamimycin A_1 by total synthesis of the enantiomer from tartaric acid[7] and also reported a revised structure (**7**) for colletodiol based upon X-ray crystallographic analysis.[8] Structures for two other similar macrocyclic antibiotics, grahamimycin A (**8**) and B (**9**) have also been determined;[9] the most potent of these, grahamimycin A



(which is in fact identical with colletoketol[10]), exhibited activity against 36 species of bacteria, eight species of blue-green algae, two species of green algae, and five fungi.

Colletodiol has been synthesized by both Seebach[11] and Mitsunobu.[12] Both groups experienced considerable difficulties, particularly in performing the final macro-

(1) This paper is respectfully dedicated to my postdoctoral mentor, Professor E. J. Corey, on the occasion of his 60th birthday and in appreciation of the opportunity to have worked with him and his exceptional research group.

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