Access to Protected 2-Alkylidene 1,3-Diones by Modified Knoevenagel Reaction in the Presence of Thiophenol. A New Approach to Spirocyclopentanol Construction

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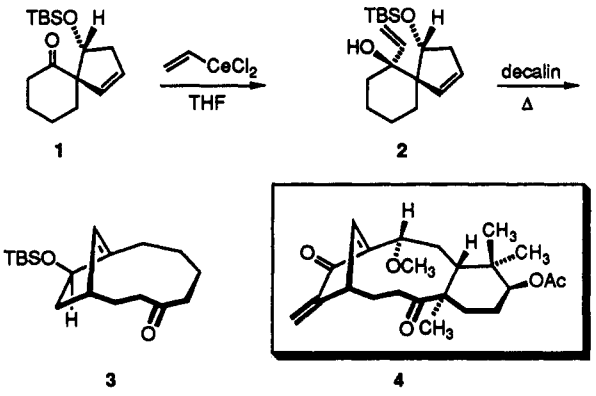
A general procedure is described for trapping the products of Knoevenagel condensation involving 1,3-diketones and aliphatic aldehydes. Simple stirring of a three-component mixture consisting of each reactant and thiophenol in dichloromethane containing silica gel leads to products in which the 2-alkylidene 1,3-dione has been intercepted to give a (most often) crystalline Michael adduct. The yields are usually quite acceptable, especially if the β-dicarbonyl compound is cyclic. Oxidation of these adducts with sodium periodate regenerates the conjugated enedione, which reacts rapidly with air to give a cyclic peroxide unless protected from the atmosphere. When a monoprotected succinaldehyde is utilized as starting material, hydrolysis of the resultant adduct in aqueous acid results in intramolecular aldolization to give a spirocyclic cyclopentanol.

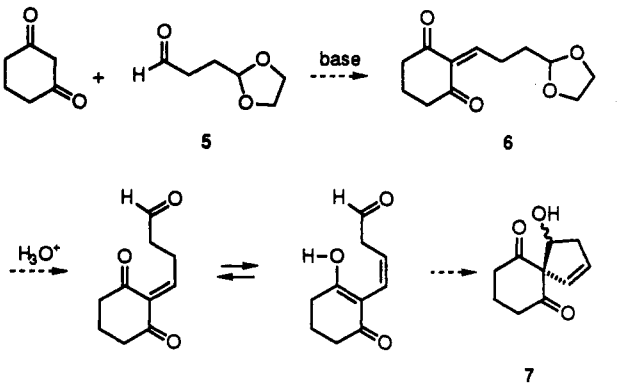
We have recently developed a direct stereocontrolled approach to the A/B subunit of the cytotoxic 8,9-seco-*ent*-kaurenes in which the diene carbinol **2** is isomerized to **3** in 92% yield when heated in decalin.[2] This model study was designed to set the stage for the ultimate acquisition of *O*-methylshikoccin (**4**)[3] and/or its structurally related antitumoregenic analogs shikodomedin,[4] rabdolatifolin,[5] and shikoccin.[6]

The spirocyclopentenol unit present in **1** was constructed via an efficient intramolecular Lewis acid-catalyzed allylsilane–carboxaldehyde condensation.[2] Unfortunately,



the superb stereoselectivity associated with this particular ring closure reaction could not be realized in more conformationally rigid trans-fused decalin systems. Described herein is an alternative protocol that meets the inherent challenge of constructing a spirocyclic cyclopentanol suitably functionalized for introduction of a double bond later in the pathway. In addition, our new method also solves the outstanding problem of carrying forward an added oxygen substituent that is destined to become the methoxyl group in **4**.

Consideration was given to a potentially suitable sequence involving condensation of a cyclic 1,3-dicarbonyl compound with a bifunctional aldehyde such as **5**. Deblocking of the Knoevenagel product **6**[7] to release a new aldehyde functional group was to be followed immediately by deprotonation and intramolecular aldol cyclization as depicted in **7**.



As attractive as this scheme might appear to be at first glance, it is flawed because of the well-recognized inability to arrest Knoevenagel reactions involving cyclic 1,3-diketones and *aliphatic* aldehydes at the monoaddition stage.[8–11] Very few adducts such as **8** have been isolated.[12] This is because these Knoevenagel products are highly reactive Michael acceptors capable of engaging the unreacted dicarbonyl reagent in kinetically rapid 1,4-addition to give bis-adducts such as **9**.[13]

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(1) Postdoctoral Fellow of the Deutsche Forschungsgemeinschaft, 1993.

(2) (a) Ladouceur, G.; Paquette, L. A. *Synthesis* **1992**, 185. (b) Paquette, L. A.; Ladouceur, G. *J. Org. Chem.* **1989**, *54*, 4278. For earlier references to the intramolecular Sakurai reaction, consult (c) Schinzer, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 308. (d) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970. (e) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.

(3) (a) Node, M.; Ito, N.; Fuji,K.; Fujita, E. *Chem. Pharm. Bull.* **1982**, *30*, 2639. (b) Node, M.; Ito, N.; Uchida, I.; Fujita, E.; Fuji, K. *Chem. Pharm. Bull.* **1985**, *33*, 1029.

(4) Fujita, T.; Takeda, Y.; Shingu, T.; Kido, M.; Taira, Z. *J. Chem. Soc., Chem. Commun.* **1982**, 162.

(5) Takeda, Y.; Fujita, T.; Ueno, A. *Phytochemistry* **1983**, *22*, 2531.

(6) (a) Fujita, E.; Ito, N.; Uchida, I.; Fuji, K.; Taga, T.; Osaki, K. *J. Chem. Soc., Chem. Commun.* **1979**, 806. (b) Nagao, Y.; Ito, N.; Kohno, T.; Kuroda, H.; Fujita, E. *Chem. Pharm. Bull.* **1982**, *30*, 727.

(7) (a) Review of carbocyclic spiro compound synthesis: Krapcho, A. P. *Synthesis* **1974**, 383. (b) For a more closely allied example, see Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361.

(8) Jones, G. *Org. React.* **1967**, *15*, 204.

(9) Nagarajan, K.; Shenoy, S. J. *Ind. J. Chem., Sect. B.* **1992**, *31*, 73.

(10) Hobel, K.; Margaretha, P. *Helv. Chim. Acta* **1989**, *72*, 975.

(11) Bolte, M. L.; Crow, W. D.; Yoshida, S. *Aust. J. Chem.* **1982**, *35*, 1421.

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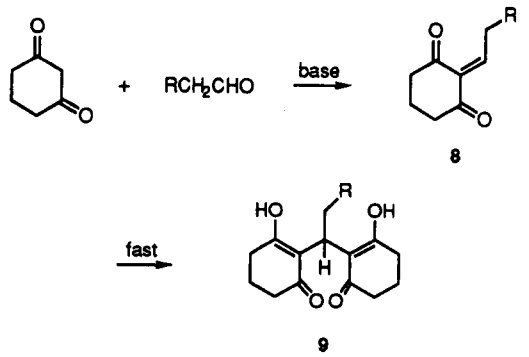


It was reasoned that should 8 be intercepted by a nucleophile which could be eliminated readily at a later stage, a workable and useful approach to 7 and functionally related molecules would be at hand. Although secondary amines have been used for this purpose,[11] we opted to utlize thiophenol on the merits of anticipated convenient extrusion of the sulfur substituent following sulfoxide formation.[14]

Results and Discussion

After preliminary attempts to execute this plan had been screened, it was discovered that the most satisfactory method for appropriate reaction was to stir the three reagents together in a dichloromethane slurry of silica gel at room temperature. Under these conditions, rapid formation of the desired product was noted, although reaction efficiency appears to be intimately associated with the relative acidity of the β-diketone and the steric hindrance resident in the aldehyde.

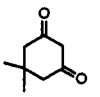
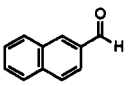
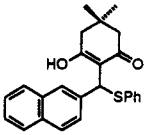
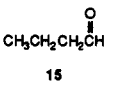
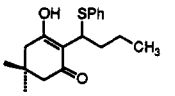
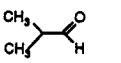
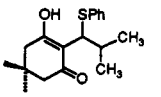
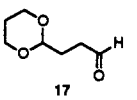
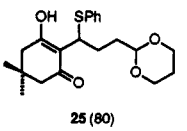
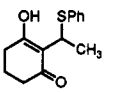
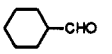
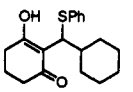
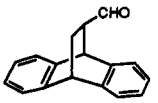
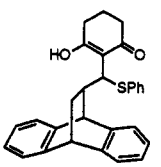
This procedure is direct and proceeds satisfactorily with a variety of aldehydes (Table 1). The obvious first 1,3-dicarbonyl substrate to examine, dimedone (**10**), was admixed initially with the aromatic substrate 2-naphthaldehyde (**14**) in order to gauge workability. This combination proved to be exemplary, as adduct **22** was formed in 97% yield without any evidence of dimer production (as in **9**). When the reaction partner was *n*-butyraldehyde (**15**), the yield of **23** dropped to 60%, and 8% of the dimer was formed competitively. A modest increase in the steric bulk of the aldehyde as in isobutyraldehyde (**16**) was sufficient to return **24** in 73% yield without coproduction of dimer. When the bifunctional electrophilic reagent **17** was analogously utilized, the desired adduct **25** was obtained in 80% yield; in line with precedent involving **15**, 11% of the dimer could also be isolated.

When the survey was extended to include 1,3-cyclohexanedione (**11**) and acetaldehyde (**18**), no significant departure in reaction efficiency was encountered. In this most stringent test of the method, dimerization was kept to only 5% despite the small size of the ethylidene group in the first-formed Knoevenagel (or alternatively acid-catalyzed aldol) product. The high yield of **26** (93%) made it clear that reduced levels of substitution in the aldehyde are conducive to the three-component condensation. In line with this analysis, we found that the involvement of cyclohexanecarboxaldehyde (**19**) and the acrolein–anthracene adduct **20** resulted in a progessive lowering of the yield of sulfide to 80 and 60%, respectively.

Cyclopentane-1,3-dione (**12**) was next evaluated (Table 2) because of the increased acidity of its enolizable proton and, more importantly, the increased nucleophilicity of its enol tautomer. At issue was whether thiophenol could compete with equal effectiveness under such circumstances. Our findings reveal that steric bulk in the aldehyde lends itself admirably to providing thiophenol the kinetic advantage. The acquisition of **29** and **32** in yields of 95 and 64%, respectively, supports this conclusion. When the level of substitution in the immediate vicinity of the aldehyde is reduced as in **15** and **21**, the procedure suffers from heightened levels of dimer formation. This pattern is the opposite of that encountered with 1,3-cyclohexanedione (**11**) and is attributed to the marked difference in nucleophilicity of the corresponding enols.

Since acetylacetone (**13**) is recognized to be the least

Table 1. Three-Component Condensation of Dimedone (10) and 1,3-Cyclohexanedione (11) with Aldehydes in the Presence of Thiophenol

1,3-dicarbonyl compd	aldehyde	adduct (% yield)	% yield of dimer (if formed)
 10	 14	 22 (97)	0
10	 15	 23 (60)	8
10	 16	 24 (73)	0
10	 17	 25 (80)	11
 11	 18	 26 (93)	5
11	 19	 27 (80)	16
11	 20	 28 (60)	33

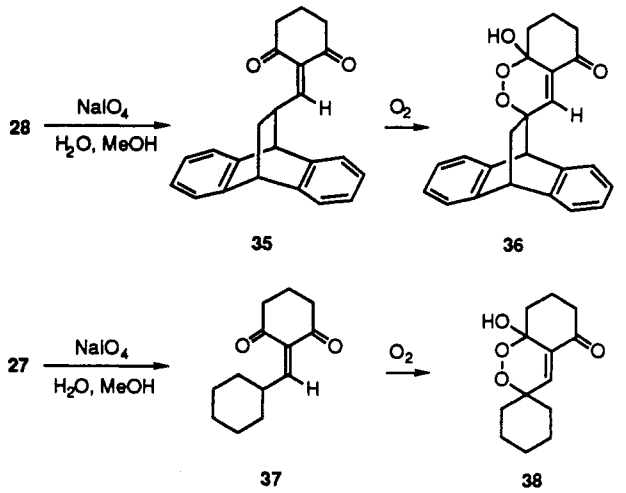
(12) (a) Margaretha, P.; Polansky, O. E. *Monatsh. Chem.* **1970**, *101*, 824. (b) Eaton, P. E.; Bunnelle, W. H. *Tetrahedron Lett.* **1984**, *25*, 23. (c) Eaton, P. E.; Bunnelle, W. H.; Engel, P. *Can. J. Chem.* **1984**, *62*, 2612.

(13) References 9–12 and Ogawa, T.; Murafuji, T.; Suzuki, H. *Chem. Lett.* **1988**, 849.

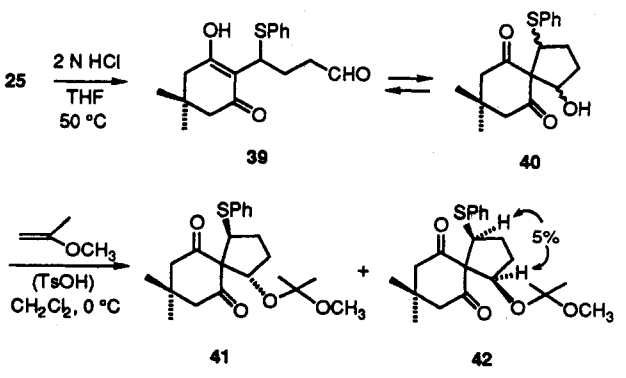
(14) Following completion of our work, we were made aware of the fact that Nawaz and co-workers had used an identical ploy to trap the products of condensation involving 4-hydroxycoumarin and benzaldehydes [Nawaz, K.; Munawar, M. A.; Siddiq, M. *J. Chem. Soc. Pak.* **1991**, *13*, 272]. The adducts were the end-products of their study.

acidic of the 1,3-diketones studied here, the capability of its enol to compete against thiophenol should be greatly reduced. Indeed, dimer formation was not competitive. However, **33** and **34** were formed only in modest yields. These findings provide convincing indication that not all 1,3-diketones are equally responsive to the Knoevenagel reaction, at least as modified in this study.

Eaton has earlier reported that elimination of thiophenol from a structurally related compound could be achieved using MCPBA as the oxidizing agent.[12c] In our hands, the olefinic diketone was not isolated and rapid conversion to bis-adducts of type **9** was observed. Highly improved results were realized when the oxidation was effected with sodium periodate in aqueous methanol. During the ensuing workup and chromatography, rapid conversion to less-polar oxygen adducts was observed. The conversion of **28** to **36** via **35** and the related production of **38** are illustrative. This heightened reactivity of **35** and **37** toward O_2 is not unusual, the phenomenon having been observed earlier by Bolte and co-workers.[11]



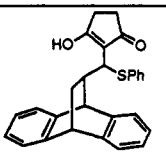
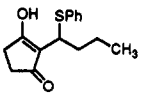
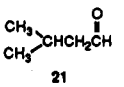
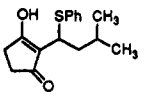
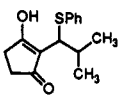
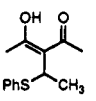
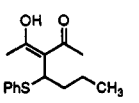
The possibility of spirocyclization was next confronted. To this end, acetal **25** was heated to 50 °C with 2 N hydrochloric acid in THF. The expectation was that the resulting aldehyde **39** would experience intramolecular aldol condensation to deliver **40**. Usually, an 18-h reaction



time was required for **25** to be totally consumed. Following chromatography to remove the 1,3-propanediol, no added effort was made to separate **39** from the diastereomeric spiro aldols **40**. Several attempts to trap **40** as its *tert*-butyldimethylsilyl ether were unsuccessful. For this reason, recourse was made instead to introducing a protecting group under acidic conditions. Reaction with 2-methoxypropene in the presence of a catalytic quantity of *p*-toluenesulfonic acid was complete within 2 h. It was possible to separate **41** from **42** by chromatographic means and to identify the stereochemistry of the two isomers by means of NOE measurements. As seen in **42**, the cis arrangement of the two indicated methine protons lends itself to an effect of significant magnitude (5%). When these hydrogens are trans-disposed as in **41**, the Overhauser effect is drastically reduced (0.5%).

Thus, it has been demonstrated that application of the Knoevenagel reaction to monoprotected succinaldehydes and a cyclic 1,3-diketone with subsequent acidic hydrolysis opens a new pathway to spirocycle construction holding the prospect of substantive utility in the synthesis of natural products.

Table 2. Thiophenol-Intercepted Knoevenagel Additions Involving Cyclopentane-1,3-dione (12) and Acetylacetone (13)

1,3-dicarbonyl compd	aldehyde	adduct (% yield)	% yield of dimer (if formed)
 12	20	 29 (95)	0
12	15	 30 (26)	28
12	 21	 31 (29)	32
12	16	 32 (64)	10
 13	18	 33 (10)	0
13	15	 34 (22)	0

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at the indicated field strengths. High-resolution mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All reactions were carried out under a nitrogen atmosphere and the ensuing separations were effected either under flash chromatography conditions on Merck silica gel HG_{254} or by MPLC on Merck LiChroprep Si60 glass columns. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried before use.

General Procedure for Three-Component Condensation. A mixture of the 1,3-diketone (200 mg, 1.00 equiv), the aldehyde

(1.70 equiv), and thiophenol (10.0 equiv) in CH_2Cl_2 (10 mL) was stirred at rt together with 3.0 g of silica gel until TLC analysis indicated no starting material remaining. The solvent was removed under reduced pressure and the resulting powder was transferred directly onto a prepacked column of silica gel (40 g). Elution with ethyl acetate in petroleum ether resulted in efficient separation of the thioether from excess reagents and the dimer when the latter was present.

For **22**: reaction time of 5 d; white solid, mp 162 °C (from ethyl acetate); IR ($CHCl_3$, cm^{-1}) 3020, 2980, 1650, 1625; ^1H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1 H), 7.85–7.79 (m, 4 H), 7.59–7.55 (m, 1 H), 7.49–7.33 (m, 4 H), 7.32–7.23 (m, 3 H), 6.33 (s, 1 H), 2.47 (d, J = 17.5 Hz, 1 H), 2.26–2.17 (m, 2 H), 2.03 (d, J = 16.0 Hz, 1 H), 1.02 (s, 3 H), 0.77 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.7, 173.3, 135.2, 133.4, 133.0, 132.9, 131.0 (2 C), 129.2 (2 C), 128.7, 128.0, 127.8, 127.6, 126.4, 126.2 (3 C), 111.7, 50.3, 46.6, 43.5, 31.7, 28.4, 27.6; MS m/z ($M^+ - C_6H_5SH$) calcd 278.1307, obsd 278.1292. Anal. Calcd for $C_{25}H_{24}O_2S$: C, 77.29; H, 6.23. Found: C, 77.12; H, 6.32.

For **23**: reaction time of 60 min; white solid, mp 122 °C (from ethyl acetate–ether); IR (KBr, cm^{-1}) 3380–3000, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 9.07 (s, 1 H), 7.35–7.14 (m, 5 H), 4.96 (t, J = 7.5 Hz, 1 H), 2.32–1.95 (m, 4 H), 1.74 (dt, J = 7.6, 7.6 Hz, 2 H), 1.44 (tq, J = 7.0, 7.0 Hz, 2 H), 0.98 (s, 3 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.69 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.1, 172.6, 132.7 (2 C), 130.9 (2 C), 128.9, 127.4, 112.9, 50.3, 43.4, 41.8, 35.6, 31.6, 28.1, 27.7, 21.1, 13.9; MS m/z (M^+) calcd 304.1497, obsd 304.1507. Anal. Calcd for $C_{18}H_{24}O_2S$: C, 71.01; H, 7.95. Found: C, 70.87; H, 7.92.

For **24**: reaction time of 3 h; white solid, mp 121 °C (from ethyl acetate); IR ($CHCl_3$, cm^{-1}) 3250–3120, 1705, 1650, 1625; ^1H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1 H), 7.30–7.14 (m, 5 H), 4.77 (d, J = 7.8 Hz, 1 H), 2.17–1.89 (m, 5 H), 1.11 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.7 Hz, 3 H), 0.99 (s, 3 H), 0.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.4, 172.6, 132.6, 131.0 (2 C), 128.9 (2 C), 127.3, 112.1, 50.4, 49.7, 43.4, 32.8, 31.5, 28.2, 27.8 21.2, 21.0; MS m/z ($M^+ - C_6H_5SH$) calcd 194.1307, obsd 194.1299. Anal. Calcd for $C_{18}H_{24}O_2S$: C, 71.01; H, 7.95. Found: C, 71.10; H, 7.97.

For **25**: reaction time of 30 min; white solid, mp 139 °C (from ethyl acetate–ether); IR ($CHCl_3$, cm^{-1}) 3300–3100, 1645, 1620, 1405; ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1 H), 7.30–7.14 (m, 5 H), 4.89 (t, J = 7.5 Hz, 1 H), 4.55 (t, J = 4.9 Hz, 1 H), 4.11–4.05 (m, 2 H), 3.79–3.70 (m, 2 H), 2.29 (d, J = 17.4 Hz, 1 H), 2.16–1.60 (m, 8 H), 1.32 (d, J = 13.4 Hz, 1 H), 0.97 (s, 3 H), 0.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.0, 172.6, 132.8, 130.8 (2 C), 128.9 (2 C), 127.3, 112.5, 101.6, 66.9 (2 C), 50.3, 43.3, 41.8, 33.1, 31.6, 28.3, 27.8, 27.6, 25.7; MS m/z ($M^+ - C_6H_5SH$) calcd 266.1518, obsd 266.1502. Anal. Calcd for $C_{21}H_{28}O_4S$: C, 66.99; H, 7.50. Found: C, 66.66; H, 7.42.

For **26**: reaction time of 2 h at 0 °C; white solid, mp 118 °C (from ether–ethyl acetate); IR ($CHCl_3$, cm^{-1}) 3250–3130, 1650, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 9.17 (br s, 1 H), 7.30–7.16 (m, 5 H), 4.98 (q, J = 7.2 Hz, 1 H), 2.29 (m, 4 H), 1.78 (m, 2 H), 1.43 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.0, 174.6, 133.1, 130.7 (2 C), 128.8 (2 C), 127.3, 115.1, 36.8, 36.4, 29.6, 20.2, 18.9; MS m/z (M^+) calcd 248.0871, obsd 248.0769. Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 67.66; H, 6.52.

For **27**: reaction time of 24 h; white solid, mp 143 °C (from ethyl acetate–hexane); IR ($CHCl_3$, cm^{-1}) 3250–3100, 1720, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 7.29–7.15 (m, 5 H), 4.80 (d, J = 8.3 Hz, 1 H), 2.45–2.16 (m, 3 H), 2.05–1.92 (m, 2 H), 1.89–1.52 (m, 7 H), 1.39–1.08 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.5, 174.3, 132.8, 131.1 (2 C), 128.8 (2 C), 127.3, 113.0, 48.6, 41.8, 36.6, 31.5, 31.3, 29.7, 26.2 (2 C), 26.1, 20.2; MS m/z ($M^+ - C_6H_5SH$) calcd 206.1304, obsd 206.1305. Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.11; H, 7.64. Found: C, 72.02; H, 7.72.

For **28**: reaction time of 2 h; white solid, mp 178 °C (from ethyl acetate–petroleum ether); IR ($CHCl_3$, cm^{-1}) 3250–3140, 1650, 1620; ^1H NMR (300 MHz, acetone-d_6) (major diastereomer) 7.92–6.94 (series of m, 13 H), 5.21 (d, J = 2.0 Hz, 1 H), 4.37 (t, J = 2.6 Hz, 1 H), 4.35 (d, J = 11.7 Hz, 1 H), 3.44–2.13 (series of m, 8 H), 1.50 (ddd, J = 12.4, 5.6, 2.4 Hz, 1 H). Anal. Calcd for $C_{29}H_{26}O_2S$: C, 79.42; H, 5.98. Found: C, 79.38; H, 6.12.

For **29**: reaction time of 14 h; white solid, mp 174–175 °C (from ethyl acetate–petroleum ether); IR ($CHCl_3$, cm^{-1}) 1720, 1630; ^1H NMR (300 MHz, acetone-d_6) (major diastereomer) δ 7.43–6.89 (m, 13 H), 4.82 (d, J = 2.1 Hz, 1 H), 4.22 (t, J = 2.6 Hz, 1 H), 3.36 (d, J = 11.7 Hz, 1 H), 2.26 (br s, 4 H), 2.15–2.06 (m, 2 H), 1.07 (ddd, J = 12.5, 5.2, 2.5 Hz, 1 H); MS m/z ($C_{14}H_{10}^+$) calcd 178.0783, obsd 178.0788.

For **30**: reaction time of 3.5 h; colorless crystals, mp 121 °C (from ethyl acetate–ether); IR ($CHCl_3$, cm^{-1}) 3300–3150, 1690, 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.16 (m, 5 H), 4.29 (t, J = 7.2 Hz, 1 H), 2.40 (s, 4 H), 1.91–1.70 (m, 2 H), 1.51–1.36 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.7, 130.4 (2 C), 128.9 (2 C), 127.1, 116.6, 42.0, 35.8, 29.8, 29.7, 20.6, 13.7 (2 C not evident because of tautomeric exchange); MS m/z ($M^+ - C_6H_5SH$) calcd 152.0837, obsd 152.0847. Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.92. Found: C, 68.39; H, 6.91.

For **31**: reaction time of 14 h; colorless crystals, mp 155 °C (from ethyl acetate–hexane); IR ($CHCl_3$, cm^{-1}) 3300–3150, 1695, 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (br s, 1 H), 7.31–7.14 (m, 5 H), 4.35 (t, J = 7.6 Hz, 1 H), 2.38 (br s, 4 H), 1.76 (sept, J = 6.6 Hz, 1 H), 1.62 (dd, J = 7.4, 7.4 Hz, 2 H), 0.97 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.1, 130.2 (2 C), 129.1 (2 C), 127.3, 117.0, 42.8, 40.5, 26.1, 22.6, 22.1 (4 C not evident because of tautomeric exchange); MS m/z (M^+) calcd 276.1184, obsd 276.1210. Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.41; H, 7.39.

For **32**: reaction time of 72 h; colorless crystals, mp 114 °C (from ethyl acetate–ether); IR ($CHCl_3$, cm^{-1}) 3700–3200, 1660, 1610, 1550; ^1H NMR (300 MHz, $CDCl_3$) δ 9.7–9.0 (very br s, 1 H), 7.30–7.16 (m, 5 H), 4.17 (d, J = 5.5 Hz, 1 H), 2.40 (s, 4 H), 2.19 (m, 1 H), 1.07 (d, J = 6.7 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.2, 130.2 (2 C), 129.1 (2 C), 127.2, 115.4, 50.3, 39.9 (4 C not evident because of tautomeric exchange); MS m/z ($M - C_6H_5SH$) calcd 152.0837, obsd 152.0844. Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.92. Found: C, 68.54; H, 6.88.

For **33**: reaction time of 6 h at 0 °C then 7 d at −10 °C; white solid, mp 48 °C (from ethyl acetate–hexanes); IR ($CHCl_3$, cm^{-1}) 1700, 1360; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2 H), 7.36–7.30 (m, 3 H), 3.85–3.75 (m, 2 H), 2.24 (s, 3 H), 2.20 (s, 3 H), 1.23 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.4, 202.1, 133.6 (2 C), 132.3, 129.1 (2 C), 128.1, 74.5, 42.4, 30.5, 28.8, 19.7. Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 66.13; H, 6.69.

For **34**: reaction time of 6 d; colorless oil; IR ($CHCl_3$, cm^{-1}) 1700, 1360; ^1H NMR (300 MHz, $CDCl_3$) 7.43–7.37 (m, 2 H), 7.33–7.24 (m, 3 H), 3.86 (d, J = 10.7 Hz, 1 H), 3.68 (dt, J = 3.6, 8.9 Hz, 1 H), 2.21 (s, 3 H), 2.18 (s, 3 H), 1.68–1.24 (m, 4 H), 0.86 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.6, 202.2, 133.3 (2 C), 132.9, 129.0 (2 C), 127.9, 73.7, 47.9, 34.6, 30.3, 29.1, 19.5, 13.6; MS m/z (M^+) calcd 264.1184, obsd 264.1198.

Aldehyde 17.[15] To a suspension of magnesium turnings (486 mg, 20.0 mmol) in anhydrous THF (1.5 mL) was added one-half of a solution of 2-(2-bromoethyl)-1,3-dioxane (3.92 g, 20.8 mmol) in the same solvent (15 mL) without stirring. 1,2-Dibromoethane (0.1 mL) was introduced and the remaining bromide solution was added dropwise during 1.5 h at 30–35 °C with stirring. Upon completion of the addition, the Grignard solution was stirred for an additional 1.5 h at this temperature and transferred via cannula into THF (2 mL) containing DMF (1.46 g) at 0 °C. The original flask was rinsed with an additional 5 mL of THF. After 15 min, the turbid solution became clear, at which point it was poured into ice-cold saturated NH_4Cl solution (80 mL) and diluted with ether (20 mL) and water (20 mL). The aqueous phase was extracted with ether (6 × 50 mL) and the combined organic layers were dried and evaporated to leave 2.21 g of a yellow oil. Kugelrohr distillation of this material at 70–110 °C and 0.2 Torr gave **17** in 38% yield; IR ($CHCl_3$, cm^{-1}) 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 1.5 Hz, 1 H), 4.58 (t, J = 4.8 Hz, 1 H), 4.07 (ddd, J = 11.8, 5.0, 1.2 Hz, 2 H), 3.72 (m, 2 H), 2.53 (td, J = 8.6, 1.5 Hz, 2 H), 2.03 (m, 1 H), 1.92 (m, 2 H), 1.31 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.0, 100.6, 66.8 (2 C), 38.1, 27.7, 25.7; MS m/z (M^+) calcd 144.0786, obsd 144.0761.

(15) This aldehyde has been previously cited in the patent literature: (a) Drautz, K.; Kleemann, A.; Samson, M. *Chem. Ztg.* **1984**, *108*, 391. (b) Kleemann, A.; Samson, M. Eur. Pat. EP 81-107463, 19 Sept 1981; *Chem. Abstr.* **1982**, *97*, 163497j. The Grignard approach described herein represents a more direct and practical synthetic entry to this intermediate.

Peroxide Formation. A. Oxidative Elimination of 28. To solution of **28** (44 mg, 0.10 mmol) in a mixture of methanol (6 mL), water (4 mL), and ether (10 mL) was added a solution of sodium periodate (24 mg, 0.11 mmol) in 1:1 methanol/water (3 mL). After being stirred for 3 h, the mixture was poured into brine and extracted with CH_2Cl_2 (3×). The combined organic layers were dried and evaporated to leave a residue that was filtered through a short column of silica gel (elution with 30% ethyl acetate in petroleum ether) and concentrated under vacuum to give **36** as a 4:1 mixture of diastereomers. The major isomer was obtained by recrystallization from CH_2Cl_2 (28 mg, 79%): colorless solid, mp 198 °C; IR ($CHCl_3$, cm^{-1}) 3590, 1720, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 1 H), 7.30 (m, 2 H), 7.18 (m, 5 H), 6.13 (s, 1 H), 4.65 (s, 1 H), 4.36 (t, J = 2.4 Hz, 1 H), 3.48 (br s, 1 H), 2.66 (m, 1 H), 2.38 (m, 1 H), 2.21–1.81(series of m, 5 H), 1.59 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.9, 143.3, 142.0, 139.8, 138.7, 138.4, 136,9, 126.9, 126.6, 126.4 (2 C), 126.0, 125.3, 123.6, 123.3, 97.2, 85.1, 52.0, 43.6, 39.4, 39.1, 31.2, 17.7; MS the molecular peak was observed but was too transient for high-resolution measurement.

B. Oxidative Elimination of 27. Sulfide **27** (38 mg, 0.12 mmol) was dissolved in a mixture of methanol (6 mL), ether (4 mL), and water (2 mL). The solution was cooled to 0 °C and sodium periodate (28 mg, 0.13 mmol) dissolved in 1:1 methanol/water (2 mL) was introduced. The mixture was allowed to warm to rt, stirred for 2 h, and diluted with water (20 mL). The aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (4×). The combined organic layers were dried, concentrated to a volume of approximately 40 mL, and stirred for 24 h while exposed to air. The solvent was evaporated under vacuum, and the resulting crystals were washed with ether/hexanes (1:1) and with petroleum ether to give **38** (25 mg, 88%): a colorless solid, mp 161–162 °C; IR ($CHCl_3$, cm^{-1}) 3450, 1700, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1 H), 3.49 (s, 1 H), 2.71–2.62 (m, 1 H), 2.39–2.27 (m, 1 H), 2.22–2.06 (m, 2 H), 2.00–1.91 (m, 2 H), 1.79–1.48 (m, 9 H), 1.42–1.31 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.4, 138.8, 136.9, 97.5, 80.2, 39.4, 32.9, 31.8, 31.0, 25.1, 21.2, 21.0, 17.7. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.45; H, 7.64.

Spirocyclization Leading to 41 and 42. To a solution of **25** (485 mg, 1.29 mmol) in THF (40 mL) was added 2 N HCl (10 mL), and the reaction mixture was heated at 50 °C for 18 h under N_2. Following dilution with water (200 mL) and extraction of the products into ether (3×), the combined organic layers were washed with brine, dried, and evaporated to leave a residue that was chromatographed on silica gel (elution with 30% ethyl acetate in petroleum ether) to give 310 mg (76%) of the **39** → **40** mixture as a colorless oil.

A 277-mg (0.87 mmol) sample of this mixture was dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0 °C. 2-Methoxypropene (1.0 mL) and a crystal of *p*-toluenesulfonic acid slurried in 0.1 mL of CH_2Cl_2 were introduced sequentially and the mixture was stirred at 0 °C for 2 h, poured into saturated Na_2HPO_4 solution (40 mL), and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried, and concentrated. MPLC of the residue on silica gel (elution with 12% ethyl acetate in petroleum ether) furnished pure **41** (78 mg, 23%) and **42** (106 mg, 31%).

For **41**: white solid, mp 176–178 °C (from benzene–petroleum ether); IR ($CHCl_3$, cm^{-1}) 1730, 1700, 1520, 1390, 1380; ^1H NMR (300 MHz, C_6D_6) δ 7.66 (m, 2 H), 7.02 (m, 2 H), 6.90 (m, 1 H), 4.72 (dd, J = 10.6, 8.5 Hz, 1 H), 4.43 (dd, J = 6.9, 6.6 Hz, 1 H), 2.84 (s, 3 H), 2.67–2.19 (series of m, 6 H), 1.88 (m, 1 H), 1.58 (m, 1 H), 1.06 (s, 3 H), 0.95 (s, 3 H), 0.86 (s, 3 H), 0.72 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.1, 204.1, 138.8, 131.2 (2 C), 129.1 (2 C), 126.6, 101.2, 80.5, 76.6, 53.9, 53.1, 50.4, 49.6, 34.2, 33.1, 30.5, 30.1, 27.3, 24.9, 24.3; MS m/z (M^+) calcd 390.1865, obsd 390.1866. Anal. Calcd for $C_{22}H_{30}O_4S$: C, 67.66; H, 7.74. Found: C, 67.41; H, 7.29.

For **42**: white solid, mp 65–67 °C; IR ($CHCl_3$, cm^{-1}) 1725, 1695, 1390, 1380; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.15 (m, 5 H), 4.23 (dd, J = 9.8, 7.6 Hz, 1 H), 4.10 (dd, J = 9.9, 9.9 Hz, 1 H), 3.13 (s, 3 H), 2.80–2.27 (series of m, 6 H), 2.08 (m, 1 H), 1.98 (m, 1 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.10 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.1, 206.9, 139.2, 131.1 (2 C), 129.1 (2 C), 126.7, 101.1, 81.9, 76.3, 56.0, 54.1, 49.4, 45.2, 31.8, 31.4, 30.5, 30.1, 27.7, 24.8 (2 C); MS m/z (M^+) calcd 390.1865, obsd 390.1852.

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