Preparation of α-Substituted *S*-Phenyl Thio Esters from Aldehydes and (Phenylthio)nitromethane

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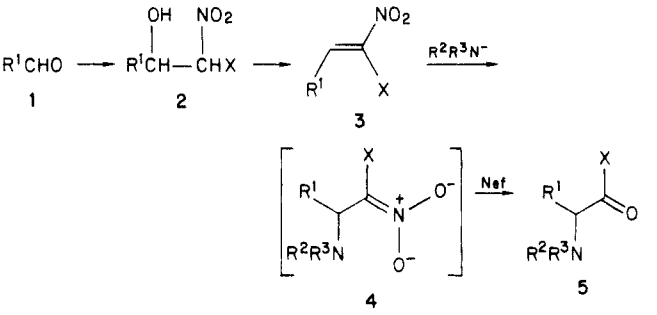
Acetaldehyde and isobutyraldehyde, RCHO, reacted with (phenylthio)nitromethane (KO-*t*-Bu, THF, *t*-BuOH) followed by methanesulfonyl chloride (Et_3N, CH_2Cl_2) to give the (*Z*)-alkenes $RCH{=}C(SPh)NO_2$. These reacted with the nucleophiles [NuM = potassium phthalimide, $CH_2FCONHK$, $PhCH_2N(Ts)Li$, MeONa, *i*-PrONa, 3β-(lithiooxy-5α-cholestane, 1,2:5,6-di-*O*-isopropylidene-3-*O*-potassio-α-D-glucofuranose, $TsNa{\cdot}H_2O$, $KCH(CO_2Me)_2$, PhLi, $PhC(OLi){=}CH_2$] in DMF, THF, or *i*-PrOH to give on subsequent ozonolysis the title thio esters (RCH(Nu)COSPh) (30–79%).

Nitroalkanes and -alkenes are versatile compounds in synthetic organic chemistry. The nitro substituent is doubly advantageous: it can control the elaboration of the carbon framework and can subsequently be transformed into a diverse array of functionality.[1] Recently we required a concise method for the conversion of aldehydes into derivatives of α-amino acids that avoided the drastic reaction conditions associated with the Strecker protocol.[2] Since nitroalkenes are powerful electrophiles,[3] we considered that a heteroatom-substituted terminal nitroalkene **3** should function as a useful amino acid precursor. In turn **3** could be readily available from **1** via **2** and the Henry reaction.[3] Thus the addition of a nitrogen-centered nucleophile to **3** should provide the nitronate salt **4**. Subsequent Nef reaction[3,4] should transform **4** into the α-amino acid derivative **5** (Scheme I). Such a synthetic protocol would be versatile since the nitrogen centered nucleophile could be replaced by a carbon-, oxygen-, or sulfur-centered species, thereby providing a general method for the homologation of aldehydes into α-substituted carboxylic acid derivatives. Herein we report experimental details[5] that demonstrate the realization of these objectives.

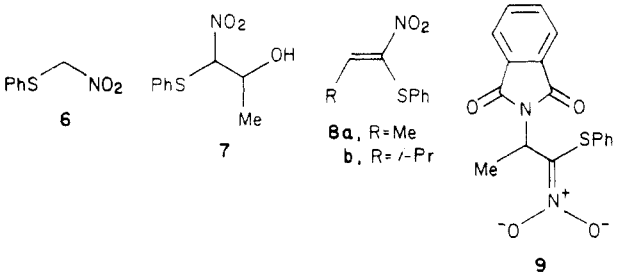
Results and Discussion

(Phenylthio)nitromethane (**6**) was prepared from (phenylthio)acetic acid by nitration of the derived dianion with propyl nitrate.[6] Following the Miyashita procedure **6** was

Scheme I



condensed with acetaldehyde in the presence of methanolic potassium hydroxide at 0 °C to produce the nitro aldol **7** as a mixture of diastereoisomers. Without purification **7** was dehydrated using methanesulfonyl chloride and triethylamine in dichloromethane solution at −78 to 0 °C to produce the geometrically pure nitroalkene **8a** (60%).



With exactly the same protocol 2-methylpropanal was converted into **8b** (31%). Since neither of these yields was especially good, we optimized the Miyashita preparation. Thus in the optimum reaction acetaldehyde was condensed with **6** in the presence of potassium *tert*-butoxide (0.1 equiv) in THF–*tert*-butyl alcohol (1:1) at 0 °C and the resultant nitroaldol dehydrated to produce **8a** (≥89%). Under these conditions 2-methylpropanal was converted into **8b** (82%).

The nitroalkene **8a** reacted smoothly with potassium phthalimide in DMF solution at −20 °C to produce the nitronate **9**. At this point in the reaction neither the dark color of the solution nor TLC behavior were favorable auspices. However, following the excellent McMurry procedure[7] the nitronate **9** was directly oxidized without isolation by using ozone at −78 °C in methanol–DMF. At this point the solution became colorless, and TLC indicated the presence of a single compound. Chromatography gave the (*RS*)-alanine derivative **10a** (68%). The oxidative

(1) For recent examples, see: *Chem. Eng. News* **1984**, *62*, 20. Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *Chem. Lett.* **1982**, 1505. Barton, D. H. R., Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098. Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Ibid.* **1982**, 551. Corey, E. J.; Estriecher, H. *Tetrahedron Lett.* **1981**, *22*, 603. Asaoka, M.; Mukuta, T.; Takei, H. *Ibid.* **1981**, 735. Knochel, P.; Seebach, D. *Ibid*, **1981**, *22*, 3223. Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149. Corey, E. J.; Samuelsson, B.; Luzzio, F. A. *Ibid.* **1984**, *106*, 3682. Nakashita, Y.; Hesse, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1021. Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210. Seebach, D.; Knochel, P. *Ibid.* **1984**, *67*, 261. Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Ibid.* **1982**, *65*, 1637. Zuger, M.; Weber, T.; Seebach, D. *Ibid.* **1980**, *63*, 2005. Aebischer, B.; Bieri, J. B.; Prewo, R.; Vasella, A. *Ibid.* **1982**, *65*, 2251. Kornblum, N.; Singh, H. K.; Kelly, W. J. *J. Org. Chem.* **1983**, *48*, 333. Kornblum, N.; Singh, H. K.; Boyd, S. D. *Ibid.* **1984**, *49*, 358. Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z.-B. *J. Am. Chem. Soc.* **1984**, *106*, 1845. Oppolzer, W.; Francotte, D.; Bättig, K. *Helv. Chim. Acta* **1981**, *64*, 478.

(2) Harusawa S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1979**, 4663 and references therein.

(3) For example, see: Coombes, R. G. In "Comprehenseive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, p 325.

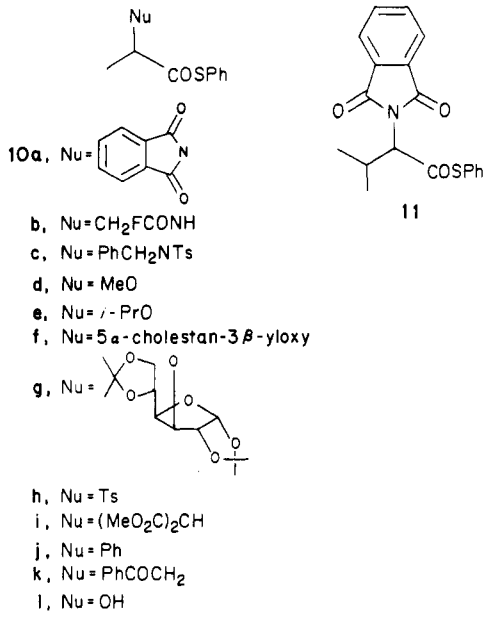
(4) For the production of acetic acid from the acid hydrolysis of chloronitromethane nitronate, see: Hawthorne, M. F.; Strahm, R. D. *J. Am. Chem. Soc.* **1957**, *79*, 3471.

(5) Banks, B. J.; Barrett, A. G. M.; Russell, M. A. *J. Chem. Soc., Chem. Commun.* **1984**, 670.

(6) Miyashita, M.; Kumezawa, T.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1978**, 362. Bordwell, F. G.; Bartmess, J. E. *J. Org. Chem.* **1978**, *43*, 3101.

(7) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259.

0022-3263/86/1951-1012$01.50/0



Nef reaction using ozone[7] is especially efficient. There exist alternative procedures for effecting the Nef reaction, all of which avoid the strongly acidic conditions associated with classical procedure.[3] These include the use of potassium permanganate,[8] singlet oxygen,[9] titanium(III) chloride,[10] $MoO_5 \cdot C_5H_5N \cdot HMPT$,[11] the recently introduced and highly selective reagent 3-carboxyliodoxylbenzene in the presence of *N-tert*-butyl-*N'*,*N'*,*N''*,*N''*-tetramethylguanidine,[12] and tributylphosphine–diphenyl disulfide.[13]

A series of nucleophiles were added to **8a** to produce the corresponding α-substituted phenyl thio ester **10** on oxidative workup (Table I). In addition **8b** was converted into the phthalimide adduct **11** (46%). The procedure was also applicable for the synthesis of *S*-phenyl 2-hydroxy(thiopropanoate) (**10l**). Thus (phenylthio)nitromethane (**6**) was condensed with acetaldehyde and, in situ under basic conditions, the Henry adduct **2** (R^1 = Me, X = SPh) was ozonolyzed to produce **10l** (58%).

Conclusion

The nitroalkenes **8a** and **8b** are clearly useful intermediates for the preparation of α-substituted *S*-phenyl thio esters by the addition of nucleophiles and ozonolysis in situ. Although none of the yields was optimized, it is clear that the procedure is readily applicable to diverse nitrogen-, oxygen-, sulfur-, and carbon functionalized thio esters. The reaction has recently been applied in an intramolecular sense in the synthesis of bicyclic β-lactams.[14]

Experimental Section

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Sargent Welch SP3-100 instrument. ^1H NMR spectra were recorded with tetramethylsilane as internal standard on a Varian EM360A, EM390A, or a Joel FX270 spectrometer. Mass spectra were recorded on a V-G 7070F mass spectrometer. Microanalyses were determined by Galbraith Laboratories, Knoxville, TN 37921. Samples for microanalyses that were oils were purified by flash chromatography, rotary evaporated, and subsequently further evaporated at ca. 0.1 mm.

Hexane and pentane were purified by distillation. THF was dried by distillation under nitrogen from potassium benzophenone ketyl. DMF and CH_2Cl_2 were respectively freshly distilled from CaH_2 and P_4O_{10}. MeOH was freshly distilled from MgI_2 and Et_3N was dried over Na wire. All reactions were carried out under dry nitrogen. Silica for chromatography refers to the Merck product Kieselgel 60 (Art. 9385).

Table I. Preparation of α-Substituted *S*-Phenyl Thio Esters

starting material	product	yield, %	starting material	product	yield, %
8a	**10a**	68	**8a**	**10h**	56
8a	**10b**	62	**8a**	**10i**	60
8a	**10c**	67	**8a**	**10j**	39
8a	**10d**	79	**8a**	**10k**	43
8a	**10e**	61	**6**	**10l**	58
8a	**10f**[a]	55	**8b**	**11**	46
8a	**10g**[a]	51			

[a] Products obtained as mixtures of diastereoisomers.

(*Z*)-1-Nitro-1-(phenylthio)propene (8a). To a solution of (phenylthio)nitromethane (**6**)[5] (2.028 g) in a mixed solvent consisting of THF/*t*-BuOH (1:1, 20 mL) was added KO-*t*-Bu as a solution in *t*-BuOH (1.0 M, 1.2 mL) at 0 °C with stirring. To the resulting creamy suspension was added freshly distilled MeCHO (4.5 mL), and stirring was continued at 0 °C for 20 min. After the reaction was quenched by pouring the solution into pH 7 buffer, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered through a 2-cm pad of silica gel, and evaporated to give 1-nitro-1-(phenylthio)propan-2-ol (**7**) (2.42 g, 95%) as an oil, which was used without further purification: ^1H NMR δ 7.35 (m, 5 H), 5.3 (dd, *J* = 3.6, 12 Hz, 1 H), 4.35 (m, 1 H), 3.0 (br d, 1 H, *J* = 12 Hz), 1.35 (dd, 3 H, *J* = 3.6, 6.3 Hz). This alcohol was subsquently dehydrated according to the procedure of Miyashita.[6] Thus, treatment with triethylamine and methanesulfonyl chloride in dichloromethane, followed by chromatography on silica gel (32 g, 50% Et_2O/hexane as eluant), gave **8a** as an oil (2.08 g, 89%): IR 3050, 1620, 1520, 1320 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.8, (q, *J* = 7.5 Hz, 1 H), 7.2 (s, 5 H), 2.1 (d, *J* = 7.5 Hz, 3 H).

(*Z*)-3-Methyl-1-nitro-1-(phenylthio)-1-butene (8b). To a solution of **6** (169 mg) in a mixed solvent consisting of THF/*t*-BuOH (1:1, 10 mL) was added KO-*t*-Bu as a solution in *t*-BuOH (1.0 M, 0.1 mL) at 0 °C with stirring. To the resulting creamy suspension was added freshly distilled Me_2CHCHO (4.0 mL) and stirring continued at 0 °C for 14 h. Following workup and filtration through silica gel, the resultant 3-methyl-1-nitro-1-(phenylthio)butan-2-ol as a mixture of diastereoisomers was used without further purification: ^1H NMR ($CDCl_3$ 90 MHz) δ 7.4 (m, 5 H), 5.5 (m, 1 H), 3.95 (m, 1 H), 2.05 (m, 1 H), 1.00 (3 d, 6 H) Dehydration to the nitroalkene was accomplished by the procedure of Miyashita[6] in a manner identical with that for **8a**. After chromatography on silica gel (10 g, eluant 5:1 hexane–Et_2O), the pure alkene was isolated as a yellow oil (185 mg, 83%): IR (neat) 1615, 1585, 1550, 1543, 1330 cm^{-1}; ^1H NMR ($CDCl_3$ 90 MHz) δ 8.54 (d, 1 H, *J* = 10 Hz), 7.22 (s, 5 H), 3.0 (m, 1 H), 1.1 (d, 6 H, *J* = 7 Hz); mass spectrum, *m/e* 223 ($M^{+\cdot}$) 177, 121.

***S*-Phenyl 2-Phthalimido(thiopropanoate) (10a).** To a stirred solution of nitroalkene **8a** (200 mg) in DMF (10 mL) at −20 °C was added potassium phthalimide (224 mg). The reaction mixture was stirred at −20 ° for ca. 30 min, diluted with MeOH (30 mL) and cooled to −78 °C. Ozone was bubbled through the reaction mixture until the solution remained blue. The reaction was then purged with nitrogen, diluted with H_2O (100 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with brine (3 × 20 mL), dried (Na_2SO_4), and evaporated. Purification by chromatography on silica (15 g, eluant, 50:50 petrol (35–60)–dichloromethane) gave **10a** (210 mg, 68%): mp 78–79 °C (from Et_2O–pentane); IR (Nujol) 1770, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.8 (m, 4 H), 7.35 (s, 5 H), 5.1 (q, 1 H, *J* = 8 Hz), 1.8 (d, 3 H, *J* = 8 Hz); mass spectrum, *m/e* 311 ($M^{+\cdot}$) 202,

(8) Wade, P. A.; Hinney, H. R.; Amin, N. V.; Vail, P. D.; Morrow, S. D.; Hardinger, S. A.; Saft, M. S. *J. Org. Chem.* **1981**, *46*, 765.
(9) Williams, J. R.; Unger, L. R.; Moore, R. H. *J. Org. Chem.* **1978**, *43*, 1271.
(10) McMurry, J. E.; Melton, J. *J. Am. Chem. Soc.* **1971**, *93*, 5309.
(11) Galobardes, M. R.; Pinnick, H. W. *Tetrahedron Lett.* **1981**, 5235.
(12) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Tetrahedron Lett.* **1983**, *24*, 5227.
(13) Barton, D. H. R. Motherwell, W. B.; Zard, S. Z. *Tetrahedron Lett.* **1984**, *25*, 3707.
(14) Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1985**, *50*, 2603.

174 (100%). Anal. Calcd for $C_{17}H_{13}NO_3S$: C, 65.59; H, 4.18. Found: C, 65.54; H, 4.33.

***S*-Phenyl 2-(Fluoracetamido)thiopropanoate (10b).** Nitroalkene (**8a**) (196 mg) was added to a solution of fluoroacetamide (160 mg) and KO-*t*-Bu (130 mg) in DMF (10 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 30 min, diluted with MeOH (30 mL), ozonized at −78 °C, and isolated as previously described. This gave **10b** (150 mg, 62%): mp 86–87 °C (from Et_2O–pentane); IR (Nujol) 3300, 1698, 1670, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (s, 5 H), 5.1 (s, 1 H), 4.9 (m, 1 H), 1.55 (d, 3 H, J = 7 Hz); mass spectrum, m/e 242 (M^+ 1), 132, 104. Anal. Calcd for $C_{11}H_{12}FNO_2S$: C, 54.77; H, 4.97. Found: C, 54.91; H, 5.09.

***S*-Phenyl 2-(*N*-Benzyltoluene-4-sulfonamido)thiopropanoate (10c).** *n*-BuLi (1.55 M, 0.71 mL) was added dropwise to $PhCH_2NHTS$ (278 mg) in THF (2.5 mL) at −10 °C. After 15 min the solution was cooled to −30 °C and **8a** (200 mg) in THF (1.0 mL) added dropwise. After 1 h at −30 °C the mixture was cooled to −78 °C, diluted with CH_2Cl_2 (35 mL), and ozonized until colorless. The reaction mixture was partitioned between CH_2Cl_2 and pH 7 phosphate buffer. The aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried and evaporated. Chromatography of the residue on silica gave (eluant 2:3 Et_2O–hexane) **10c** (289 mg, 67%) as an oil: IR (film) 3150–2880, 1701, 1341, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.75 (d, 2 H, J = 7.5 Hz), 7.3 (m, 12 H), 4.8 (q, 1 H, J = 8 Hz), 4.5 (s, 2 H), 2.35 (s, 3 H), 1.3 (d, 3 H, J = 8 Hz); mass spectrum, m/e 426 (M^+·), 288, 198. Anal. Calcd for $C_{23}H_{23}NO_3S_2$: C, 64.90; H, 5.46. Found: C, 64.89; H, 5.56.

***S*-Phenyl 2-Methoxy(thiopropanoate) (10d).** To a solution of Na (24 mg) in MeOH (10 mL) at −20 °C was added **8a** (200 mg). After being stirred for 30 min, the reaction mixture was diluted with MeOH (30 mL), ozonized at −78 °C, and isolated as previously described. Purification by chromatography on silca (10 g, eluant 1:1 CH_2Cl_2–pentane) afforded **10d** (156 mg, 79%) as a clear oil: IR (film) 1705, 1125, 1110, 950 cm^{-1}; ^1H NMR ($CDCl_3$ 90 MHz) δ 7.4 (s, 5 H), 3.9 (q, 1 H, J = 7 Hz), 3.5 (s, 3 H), 1.4 (d, 3 H, J = 7 Hz); mass spectrum, m/e 196 (M^+·), 168, 109, 59 (100%). Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.22; H, 6.12. Found: C, 61.49; H, 6.26.

***S*-Phenyl 2-Isopropoxy(thiopropanoate) (10e).** To a stirred solution of *i*-PrOH (20 mL) and Na (24 mg) at −20 °C was added **8a** (200 mg). The reaction mixture was stirred at −20 °C for 1 h, diluted with *i*-PrOH (30 mL), cooled to −78 °C, ozonized, and isolated as previously described. Purification by chromatography on silica (10 g) gave (eluant 1:1 CH_2Cl_2– pentane) **10e** (136 mg, 61%) as a clear oil: IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.2 (s, 5 H), 4.14 (q, 1 H, J = 7 Hz), 3.82 (m, 1 H), 1.18 (m, 9 H); mass spectrum, m/e 224 (M^+·), 196, 110, 109, 87 (100). Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.28; H, 7.14. Found: C, 64.46; H, 7.25.

3β-[1-((Phenylthio)carbonyl)ethoxy]-5α-cholestane (10f). *n*-BuLi (1.55 M, 610 μL) was added dropwise to 5α-cholestan-3β-ol (352 mg) in THF (3 mL) at 0 °C. After 10 min the solution was cooled to −30 °C and **8a** (176 mg) in THF (1.5 mL) was added dropwise. After 20 min the solution was cooled to −78 °C, diluted with CH_2Cl_2 (40 mL), and ozonized to a pale blue-green end point. Workup and chromatography on silica (20 g) gave (eluant 1:9 Et_2O–hexane) **10f** (266 mg, 55%) as a solid: mp 108–109 °C (from Et_2O/pentane); IR (film) 2932, 2866, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (m, 5 H), 4.1 (q, 1 H, J = 6.5 Hz), 3.35 (m, 1 H); 1.35 (d, J = 6 Hz, 3 H), 1.2 (s, 3 H), 0.8 (d, J = 6 Hz, 6 H), 0.65 (s 3 H); mass spectrum, m/e [M^+· absent] 481, 415. Anal. Calcd for $C_{36}H_{56}O_2S$: C, 78.18; H, 10.23. Found: C, 78.45; H, 10.34.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-[1-((phenylthio)carbonyl)ethyl]-α-D-glucofuranose (10g). 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (288 mg) in THF (2 mL) was added to KH (0.154 g) in THF (5.0 mL) at 0 °C. After 20 min the suspension was allowed to settle and the supernatant liquid added (via syringe) to **8a** (185 mg) in THF (1 mL) at −30 °C. After 5 min the brown solution was cooled to −78 °C, diluted with CH_2Cl_2 (25 mL), and ozonized to a faint blue and point. Workup and chromatography on silica gave (eluant 1:3 Et_2O–hexane) **10g** (217 mg, 51%) as a mixture of two diastereoisomers. The less polar isomer (110 mg, 26%, R_f 0.33 silica 1:3 Et_2O–hexane) was an oil: IR (film) 2986, 1704, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.3 (s, 5 H), 5.85 (d, 1 H, J = 2.7 Hz), 4.8 (d, 1 H, J = 3.2 Hz), 4.4–3.9 (m, 7 H), 1.54 (s, 3 H), 1.51, (d, 3 H, J = 6 Hz), 1.38 , (s, 3 H), 1.35 (s, 3 H); mass spectrum, m/e 425 (M^+·). The more polar isomer (107 mg, 25%, R_f 0.22) was an oil: IR (film) 2990, 1704, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.35 (s, 5 H), 5.95 (d, 1 H, J = 2 Hz), 4.7–3.9 (m, 8 H), 1.40 (s, 3 H), 1.35 (d, 3 H, J = 6 Hz), 1.31 (s, 3 H), 1.24 (s, 3 H), 1.22 (s, 3 H). The mixture of diastereoisomers were obtained microanalytically pure. Anal. Calcd for $C_{15}H_{28}O_7S$: C, 59.40; H, 6.66. Found: C, 59.28; H, 6.83.

***S*-Phenyl 2-(Toluene-4-sulfonyl)thiopropanoate (10h).** To a stirred solution of **8a** (200 mg) in DMF (12 mL) at −20 °C was added $TsNaH_2O$ (218 mg). The reaction mixture was stirred at −20 °C for 1 h, diluted with methanol (30 mL), cooled to −78 °C, and ozonized. Workup and chromatography on silica (10 g) gave (eluant CH_2Cl_2) **10h** (183 mg, 56%): mp 99–101 °C (from Et_2O–hexane); IR (Nujol) 1700, 1600, 1150, 1090, 935 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.82 (d, 2 H, J = 8 Hz), 7.4 (m, 7 H), 4.28 (q, 1 H, J = 7 Hz), 2.45 (s, 3 H), 1.65 (d, 3 H, J = 7 Hz); mass spectrum, m/e 322, 321, 320 (M^+), 211, 155 (100). Anal. Calcd for $C_{16}H_{16}O_3S_2$: C, 59.96% H, 499. Found: C, 59.77; H, 4.97.

Methyl 2-(Methoxycarbonyl)-3-[(phenylthio)carbonyl]-butanoate (10i). To a stirred solution of dimethyl malonate (163 mg) in DMF (12 mL) at −20 °C was added KO-*t*-Bu (150 mg). The reaction mixture was stirred at −20 °C for 20 min, and **8a** (200 mg) in DMF (1 mL) was added. After 30 min the reaction mixture was diluted with MeOH (30 mL), cooled to −78 °C, and ozonized. Workup and chromatography on silica (10 g) gave (eluant 1:1 CH_2Cl_2–pentane) **10i** (184 mg, 60%) as a clear oil: IR (neat) 1745, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$ 90 MHz) δ 7.4 (s, 5 H), 3.8 (s, 3 H), 3.78 (s, 3 H), 3.6 (m, 2 H), 1.38 (d, 3 H, J = 7 Hz); mass spectrum, m/e 298, 297 (M^+ + 1), 187 (100). Anal. Calcd for $C_{14}H_{16}O_5S$: C, 56.76; H, 5.41. Found: C, 56.90; H, 5.28.

***S*-Phenyl 2-Phenyl(thiopropanoate) (10j).** Nitroalkene **8a** (202 mg) in dry THF (2 mL) was added dropwise to PhLi (3 M, 400 μL) in THF (1.0 mL) at −110 °C. After 25 min MeOH (50 mL) was addded and the brown solution ozonized. Workup and chromatography on silica (25 g) gave (eluant 1:19 Et_2O–hexane) **10j** (86 mg, 39%) as an oil: IR (film) 3061–2931, 1698, 932 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.3 (m, 10 H), 3.95 (q, 1 H, J = 6 Hz), 1.55 (d, 3 H, J = 6 Hz); mass spectrum m/e 242 (M^+·), 133, 105, 77. Anal. Calcd for $C_{15}H_{14}OS$: C, 74.33; H, 5.83. Found: C, 74.04; H, 6.06.

***S*-Phenyl 2-Methyl-4-oxo-4-phenyl(thiobutanoate) (10k).** PhAc (120 mg) was added dropwise to lithium diisopropylamide in THF (from *n*-BuLi (1.3 M, 0.77 mL), THF (2.0 mL) and *i*-Pr_2NH (140 μL)) at −78 °C. After the mixture was warmed up to 0 °C and recooled to −30 °C **8a** (205 mg) in THF (1 mL) was added. After 10 min the brown solution was cooled to −78 °C, diluted with CH_2Cl_2 (25 mL), and ozonized to a pale blue end point. Workup and chromatography on silica (20 g) gave (eluant 1:4 Et_2O–hexane) **10k** (122 mg, 43%) as a tan solid: mp 76–77 °C (from Et_2O/hexane); IR (film) 3100–2900, 1706, 1684, 955 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.9 (m, 2 H), 7.5 (m, 8 H), 3.6–3.4 (m, 2 H), 3.06 (dd, 1 H, J = 16.7, 5.4 Hz) 1.38 (d, 3 H, J = 5.4 Hz); mass spectrum m/e [M^+· absent] 175, 105, 77. Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.79; H, 5.68. Found: C, 71.47; H, 5.32.

***S*-Phenyl 2-Hydroxy(thiopropanoate) (10l).** To a stirred solution of KOH (109 mg) and **8a** (300 mg) in methanol (20 mL) at −20 °C was added MeCHO (118 mg). After 8 h at −20 °C, the reaction mixture was cooled to −78 °C and ozonized. Workup and chromatography on silica (13 g) gave (eluant CH_2Cl_2) **10l** (186 mg, 58%) as a clear oil: IR (film) 3420, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (s, 5 H), 4.43 (q, 1 H, J = 7 Hz), 2.8 (br s, 1 H), 1.5 (d, 3 H, J = 7 Hz); mass spectrum, m/e 184, 183 (M^+ + 1, 100). Anal. Calcd for $C_9H_{10}O_2S$: C, 59.34; H, 5.49. Found: C, 58.95; H, 5.55.

***S*-Phenyl 2-Phthalimido-3-methyl(thiobutanoate) (11).** To a stirred solution of **8b** (223 mg) in DMF (12 mL) at 20 °C was added potassium phthalimide (224 mg). The reaction mixture was stirred at −20 °C for ca. 1 h, diluted with MeOH (30 mL), and ozonized at −78 °C. Workup and chromatography on silica (10 g) gave (eluant 3:1 CH_2Cl_2–hexane) **11** (130 mg, 46%): mp 99–100 °C (from Et_2O–pentane); IR (Nujol) 1780, 1765, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.82 (m, 4 H), 7.37 (s, 5 H), 4.7 (d, 1 H, J = 9 Hz), 2.9 (m, 1 H), 1.2 (d, 1.5 H, J = 7 Hz), 0.9 (d, 1.5 H, J = 7 Hz); mass spectrum, m/e 368 (impurity), 340 (M^+ + 1),

230, 202. Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.25; H, 5.01. Found: C, 67.16; H, 5.05.

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Registry No. 1 (R′ = Me), 75-07-0; 1 (R′ = Me_2CH), 78-84-2; **2** (R′ = Me_2CH, X = SPh), 100683-56-5; **6**, 60595-16-6; **7**, 67808-90-6; **8a**, 67808-91-7; **8b**, 92339-58-7; **10a**, 92339-69-0; **10b**, 92339-70-3; **10c**, 100683-57-6; **10d**, 92339-67-8; **10e**, 92339-68-9; **10f**, 100683-58-7; **10g** (isomer 1), 100683-59-8; **10g** (isomer 2), 100683-60-1; **10h**, 92339-71-4; **10i**, 92339-72-5; **10j**, 100683-61-2; **10k**, 100683-62-3; **10l**, 92339-75-8; **11**, 92339-73-6; FCH_2CONH_2, 640-19-7; $PhCH_2NHTs$, 1576-37-0; TsNa, 657-84-1; $MeO_2CCH_2CO_2Me$, 108-59-8; PhAc, 98-86-2; potassium phthalimide, 1074-82-4; 5α-cholestan-3b-ol, 80-97-7; 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, 582-52-5.

Stereocontrolled Synthesis of Polyfunctionalized *trans*-Hydrindan Systems: A Model Study toward Anisatin

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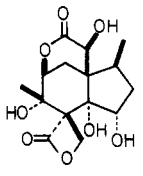
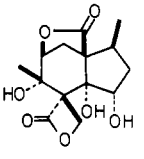
A model study toward the synthesis of anisatin (1) and its derivative, noranisatin (2), is described. A γ-lactone triol **3**, a model compound of **2**, has been prepared in highly regio- and stereocontrolled manners. Treatment of an enone **4** with osmium tetraoxide gives an angularly functionalized *trans*-hydrindan derivative **5**, which is converted into an olefinic acetate **9** by a four-step procedure. Epoxidation of **9** with *m*-CPBA and subsequent methanolysis give a cyclic ether **11**. Reaction of a ketone **12**, obtained from **11** by Collins oxidation, with methylmagnesium iodide gives almost exclusively the desired alcohol **13a**, while the reaction of **12** with methyllithium gives the undesired alcohol **13b** as a major product. The desired alcohol **13a** is transformed into **3** by a two-step sequence involving ruthenium tetraoxide oxidation of the tetrahydrofuran ring in **13a**. The stereostructures of **13a** and **13b** were unambiguously established by X-ray crystallographic analysis of crystalline **13b**.

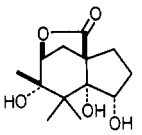
Anisatin (1), a poisonous principle isolated from the seeds of Japanese star anise, *Illicium Anisatum L.* (Shikimi in Japanese), is a highly oxygenated sesquiterpene having an unusual spiro-β-lactone ring.[1,2] The structure of **1** was elucidated in 1965 by chemical and spectral means coupled with X-ray analysis of a derivative of **1**.[2] Noranisatin (**2**), an oxidation product of **1**, played an important role in the structural determination.[2] Anisatin (**1**) has been known as one of the most toxic compounds of plant origin and furthermore, recent neurochemical studies have shown **1** to be the specific antagonist of γ-aminobutyric acid (GABA).[3]



1



2

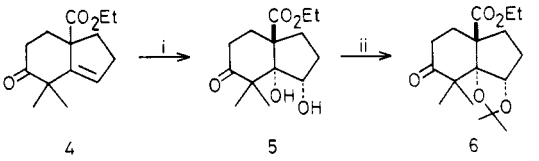


3

The unique structure and characteristic biological properties of anisatin (**1**) prompt us to attempt the total synthesis of **1**. Although anisatin (**1**) has not yet been prepared by total synthesis, a model study toward **1** has been reported recently.[4]

In this paper, we report our own model studies directed toward the synthesis of **1** and **2**. We present here a stereocontrolled construction of a polyfunctionalized *trans*-hydrindan skeleton, which possesses five asymmetric centers with desired functionality and correct stereo-

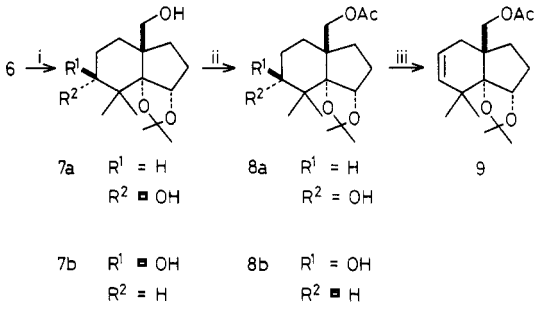
Scheme I[a]



4 5 6

[a] Reagents: i, OsO_4; ii, 2-methoxypropene, H^+.

Scheme II[a]



7a R¹ = H, R² = OH; 8a R¹ = H, R² = OH; 9

7b R¹ = OH, R² = H; 8b R¹ = OH, R² = H

[a] Reagents: i, $LiAlH_4$; ii, Ac_2O, pyridine; iii, $POCl_3$, pyridine.

(1) Lane, J. F.; Koch, W. T.; Leeds, N. S.; Gorin, G. *J. Am. Chem. Soc.* **1952**, *74*, 3211.

(2) (a) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron Lett.* **1965**, 4785. (b) Sakabe, N.; Hirata, Y.; Furusaki, A.; Tomiie, Y.; Nitta, I. *Tetrahedron Lett.* **1965**, 4795. (c) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron Lett.* **1965**, 4797. (d) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199.

(3) Kudo, Y.; Oka, J.; Yamada, K. *Neurosci. Lett.* **1981**, *25*, 83.

(4) Lindner, D. L.; Doherty, J. B.; Shoham, G.; Woodward, R. B. *Tetrahedron Lett.* **1982**, *23*, 5111. **Note Added in Proof**: The synthesis of (±)-8-deoxyanisatin has been reported after submission of our article, see: Kende, A. S.; Chen, J. *J. Am. Chem. Soc.* **1985**, *107*, 7184. See also: Kato, M.; Kitahara, H.; Yoshikoshi, A. *Chem. Lett.* **1985**, 1785.

0022-3263/86/1951-1015$01.50/0