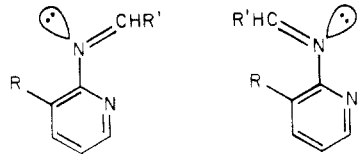
Table I. *s*-Triazolo[1,5-*a*]pyridines and *s*-Triazolo[5,1-*a*]isoquinoline

compd	R	yield, % from 7	yield, % from 8 or 11	mp, °C	formula
9a	8-CH_3	84	87	50-52[a]	$C_7H_7N_3$
9b	7-CH_3	38	26	77-79[b]	$C_7H_7N_3$
9c	6-CH_3	54	35	66-69[c]	$C_7H_7N_3$
9d	H	34		103-104.5[d]	$C_6H_5N_3$
12			83	93-95[e]	$C_{10}H_7N_3$

[a] Lit.[11] mp 51 °C. [b] Lit.[11] mp 79 °C. [c] Lit.[11] mp 57-58 °C. [d] Lit.[11] mp 102-103 °C. [e] Lit.[14] mp 95-96.5 °C.

methods. The formimidates **7** and formamidines **8** and **11** then reacted with HSA in methanol in the presence of pyridine to give *s*-triazolo[1,5-*a*]pyridines **9** and *s*-triazolo[5,1-*a*]isoquinoline (**12**) in 26–87% yields. Formimidate **7a** and formamidines **8a** and **11** gave *s*-triazolo[1,5-*a*]pyridine (**9a**) and *s*-triazolo[5,1-*a*]isoquinoline (**12**) in excellent yields (83–87%). Other formimidates (**7b–d**) and formamidines (**8b–c**) gave *s*-triazolo[1,5-*a*]pyridines **9b–d** in lower yields (26–54%) due to a concomitant formation of 2-pyridinecarbamonitriles **10**[9] which were removed by treating the crude product with sodium hydroxide solution. Because of the predominance of geometrical isomer A over B for **7a**, **8a**, and **11**, a smaller



A B

decrease in entropy of activation (ΔS^*), relative to the parent system, for the formation of *s*-triazoloazines **9a** and **12** completely eliminates the competing side reaction for the formation of cyanamides. Presumably, the reaction proceeds by replacing the dimethylamino or ethoxyl moiety with HSA followed by cyclization.

2-Unsubstituted *s*-triazolo[1,5-*a*]pyridines have been synthesized by the following methods: (1) amination of 2-aminopyridine with HSA, followed by ring-closure with formic acid in ~30% overall yield;[10,11] (2) reaction of 2-aminopyridine with DMF dimethyl acetal, followed by reaction with hydroxylamine and cyclization with polyphosphoric acid in 54% overall yield;[12] (3) reaction of *N*-iminopyridine with liquid hydrogen cyanide in 2% yield;[10] (4) rearrangement of *s*-triazolo[4,3-*a*]pyridine with base in 65% yield.[13] *s*-Triazolo[5,1-*a*]isoquinoline has been prepared by rearrangement of *s*-triazolo[3,4-*a*]isoquinoline under basic conditions in 37% yield.[14]

Our new synthetic method provides a useful alternative to literature methods and is particularly effective for the synthesis of 8-methyl-*s*-triazolo[1,5-*a*]pyridine (**9a**) and *s*-triazolo[5,1-*a*]isoquinoline (**12**) (see Table I).

Experimental Section

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analyses were dried over phosphorus pentoxide under high vacuum for 1–10 h. IR spectra were measured on a Perkin-Elmer spectrophotometer (Model 21). NMR spectra were determined with a Varian Model HA-100 spectrometer; chemical shifts (δ) are in parts per million relative to internal tetramethylsilane. Mass spectra were recorded on AEI MS 902. Ethyl formimidates **7**[7] and *N',N'*-dimethylformamidines **8** and **11**[8] were synthesized by the reported methods.

8-Methyl-*s*-triazolo[1,5-*a*]pyridine (9a). The following is a typical procedure for **9a–d** and **12** except that in the case of **9b–d** the dichloromethane solution of the crude product was washed with 30 mL of 1 N sodium hydroxide solution to remove the 2-pyridinecarbamonitrile. To a solution of 6.52 g (0.040 mol) of **8a** in a mixture of absolute methanol (60 mL) and pyridine (6.4 mL) at 0 °C was added rapidly a solution of 4.96 g (0.044 mol) of hydroxylamine-*O*-sulfonic acid in 40 mL of absolute methanol. After the mixture was stirred at room temperature for 1 h, the solvents were removed under reduced pressure at room temperature to leave a residue which was partitioned between 150 mL of dichloromethane and 30 mL of cold 3 N sodium hydroxide solution. The aqueous layer was extracted with another 50 mL of dichloromethane. The combined dichloromethane solution was washed with 30 mL of water and dried over sodium sulfate. After removal of the dichloromethane, the colorless residue (4.95 g, 93%; mp 48–51 °C) was recrystallized from hexane to give 4.6 g (87%) of **9a** as colorless crystals: mp 50–52 °C (lit.[11] mp 51 °C); ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3 H), 6.94 (t, J = 7.0 Hz, 1 H), 7.30 (d, J = 7.0 Hz, 1 H), 8.34 (s, 1 H), 8.46 (d, J = 7.0 Hz, 1 H); IR (KBr) 1630, 1500, 1345, 1310, 1260, 1200, 760 cm^{-1}; mass spectrum, m/e 133 (M^+; calcd for $C_7H_7N_3$ m/e 133.15).

Acknowledgment. The authors thank Dr. W. Gore and Mr. G. Morton and staff for the measurement and interpretation of spectral data and Mr. L. Brancone and staff for microanalyses.

Registry No. 7a, 3189-28-4; **7b**, 33842-51-2; **7c**, 65258-06-2; **7d**, 33842-49-8; **8a**, 36172-55-1; **8b**, 36172-54-0; **8c**, 36172-53-9; **8d**, 17175-39-2; **9a**, 4931-18-4; **9b**, 4999-42-2; **9c**, 4931-24-2; **9d**, 274-85-1; **11**, 76999-01-4; **12**, 234-75-3.

(8) Bredereck, H.; Effenberger, F.; Hoffmann, A. *Chem. Ber.* **1964**, *97*, 61.
(9) In addition to **9d**, the reaction of **7d** with HSA gave 2-pyridinecarbamonitrile as colorless crystals: mp 161–162 °C (lit.[15] mp 163 °C); ^{1}H NMR (Me_2SO-d_6) δ 6.69 (t, J = 6.0 Hz, 1 H), 7.02 (d, J = 9.0 Hz, 1 H), 7.6–7.9 (m, 2 H); IR (KBr) 2150 cm^{-1} (NC≡N).
(10) Okamoto, T.; Hirobe, M.; Tamai, Y.; Yabe, E. *Chem. Pharm. Bull.* **1966**, *14*, 506.
(11) Potts, K. T.; Burton, H. R.; Bhattacharyya, J. *J. Org. Chem.* **1966**, *31*, 260.
(12) Polanc, S.; Vercek, B.; Sek, B.; Stanovnik, B.; Tisler, M. *J. Org. Chem.* **1974**, *39*, 2143.
(13) Potts, K. T.; Burton, H. R.; Roy, S. K. *J. Org. Chem.* **1966**, *31*, 265.
(14) Hoogzand, C. *Recl. Trav. Chem. Pays-Bas* **1971**, *90*, 1225.
(15) Charonnat, R.; Le Perdriel, F. *Ann. Pharm. Fr.* **1968** *26*, 469.

Efficient Synthesis of the Gossypol Binaphthyl Backbone[1]

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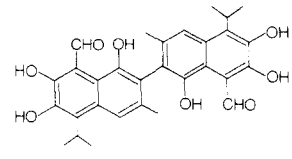
The polyphenolic binaphthyl gossypol (**1**) is well-known



Gossypol, 1

as a major constituent of cottonseed pigment. The elegant synthetic and degradative studies of Adams and Edwards, in particular the total synthesis by the latter, remain the most significant efforts in this area.[2] Interest in this

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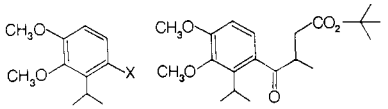
compound has been renewed of late because of reports from the People's Republic of China concerning its efficacy as a male antifertility agent.[3] A daily oral dose of 20 mg of gossypol acetate or gossypol formate caused sperm counts to drop to contraceptive levels without an accompanying decrease in testosterone levels. A monthly maintenance dosage of approximately 200 mg was sufficient in 99.89% of the 4000 men tested, giving an annual contraceptive dosage of about 3 g per man. Side effects were found to be minimal. In addition, a recent report indicates that the compound is not mutagenic, as determined in the Ames salmonella microsome test.[4] While these results are at best preliminary, gossypol has to be considered an important new lead in male contraception.[5] Herein an efficient synthesis of the binaphthyl backbone of 1 is described.

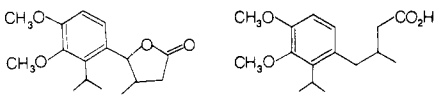
Bromobenzene 2, prepared in quantity by minor variation of published procedure,[2b,c] was Grignard formylated with DMF in the presence of EtMgBr as a transfer agent[6] to yield benzaldehyde 3 in 80%.[2c] Conversion of 3 to the corresponding $OSiMe_3$ cyanohydrin, using Me_3SiCN and ZnI_2, followed by deprotonation with *n*-butyllithium generated the acyl anion equivalent of 3. Conjugate addition to *tert*-butyl crotonate in ether at −78 °C[7] gave an intermediate $OSiMe_3$ keto cyanohydrin, directly decomposed by exposure to fluoride ion to afford the keto ester 4 in



2 X=Br
3 X=CHO

4

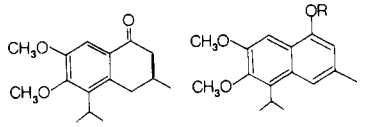
88% yield after distillation and crystallization. The *tert*-butyl ester functionality, which significantly increased the yield of conjugate addition product over that observed with the corresponding methyl ester, was then exploited as an easily removable protective group. Simultaneous ester cleavage and ketone reduction of 4 was effected by hydrogenation over Pd–C in a mixture of acetic acid and perchloric acid[8] to give acid 6 essentially quantitatively.[9] The reaction proceeds via immediate *tert*-butyl ester cleavage and ketone reduction to give butyrolactone 5.



5 6

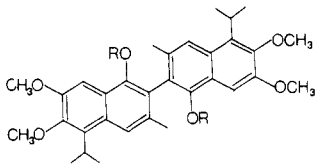
The masked *p*-methoxybenzyl ester moiety of 5 then undergoes acid-catalyzed cleavage and reduction to give the observed product 6. For this reason, other methods of ketone reduction unable to effect the intermediate ester reduction failed to give acid 6. Cyclization of the crude acid 6 with PPE in dichloromethane[10] afforded the crystalline tetralone 7 in 86% yield from keto ester 4.

The basic functionality required for final construction of the gossypol backbone is incorporated into tetralone 7.



7 8 R=Ac 9 R=H

Conversion of 7 to the corresponding enol acetate with isopropenyl acetate and a catalytic amount of H_2SO_4 in refluxing toluene, followed by in situ dehydrogenation using *o*-chloranil,[11] gave naphthyl acetate 8 in 98% yield. Reductive cleavage of acetate 8 with $NaBH_4$ in DME[12] afforded the sensitive naphthol 9 in 96% yield. Naphthol 9 undergoes a facile dimerization via phenolic coupling, an efficient manner in which to generate the binaphthyl skeleton. On the basis of literature procedure, apogossypol hexamethyl ether 11, the penultimate intermediate in the former synthesis,[2e] was obtained in 87% from 9 by dimerization to 10 followed by methylation. The overall yield of 11 from 2 is 50%, in marked contrast to the 5% obtained previously, providing a viable and flexible entry into the gossypol binaphthyl system.



10 R = H
11 R = CH_3

Experimental Section

Melting points were determined on a Fisher-Johns hot stage and are uncorrected. ^1H NMR spectra were recorded as $CDCl_3$ solutions on a Varian EM 360 60-MHz instrument. Chemical shifts are reported in δ values relative to internal $(CH_3)_4Si$ and are ±0.05 ppm. ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on a Bruker WH-90 instrument with $(CH_3)_4Si$ as internal standard. Infrared spectra, reported in reciprocal centimeters, were recorded as KBr pellets, unless otherwise noted, on a Perkin-Elmer 237B instrument. Low-resolution mass spectra were obtained by electron impact on an Atlas CH-7 spectrometer. Elemental analyses and all spectral determinations were performed by the Syntex Research Analytical Department.

All synthetic binaphthyl derivatives described below are racemic.

1-Bromo-2-isopropyl-3,4-dimethoxybenzene (2). Bromobenzene 2 was produced in 91% overall yield from 3-methoxysalicylic acid (Aldrich) by methylation (dimethyl sulfate/K_2CO_3/acetone), Grignard addition (CH_3MgCl/THF), dehydration (H_2SO_4), reduction (H_2/RaNi), and bromination (Br_2/CCl_4), following the general scheme of the published procedures.[2b,c]

2-Isopropyl-3,4-dimethoxybenzaldehyde (3). Aldehyde 3 was prepared by Grignard formylation in THF of bromide 2, using DMF according to the general method of Nelson and Uschak:[6] yield 75–88%: bp 100–105 °C (0.15 mm) [lit.[2c] bp 98–102 °C (0.13 mm)]; NMR 10.40 (s, 1 H), 7.80 (d, 1 H, J = 9 Hz), 7.00 (d, 1 H, J = 9 Hz), 4.10 (sept, 1 H, J = 6 Hz), 4.00 (s, 3 H), 3.90 (s, 3 H), 1.45 (d, 6 H, J = 6 Hz); IR (neat film) 2950, 2700, 1675, 1575, 1450, 1200, 1140, 1050, 1030, 960, 850.

***tert*-Butyl 3-Methyl-4-oxo-4-(2-isopropyl-3,4-dimethoxyphenyl)butyrate (4).** To a solution of aldehyde 3 (125 g, 600

(2) (a) Adams, R.; Geissman, T. A.; Edwards, J. D. *Chem. Rev.* **1960**, *60*, 555. (b) Edwards, J. D.; Cashaw, J. L. *J. Org. Chem.* **1955**, *20*, 847; (c) *J. Am. Chem. Soc.* **1956**, *78*, 3821; (d) *Ibid.* **1957**, *79*, 2283; (e) Edwards, J. D. *Ibid.* **1958**, *80*, 3798; (f) *J. Am. Oil. Chem. Soc.* **1970**, *47*, 441.

(3) National Coordinating Group on Male Antifertility Agents (PRC). *Chinese Med. J.* **1978**, *4*, 417.

(4) dePeyster, A.; Wang, Y. Y. *N. Engl. J. Med.* **1979**, *301*, 275.

(5) Djerassi, C. "The Politics of Contraception"; Norton: New York: 1979; Chapters 7 and 10.

(6) Nelson, D. J.; Uschak, E. A. *J. Org. Chem.* **1977**, *42*, 3308.

(7) Hunig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 302.

(8) Horning, E. C.; Reisner, D. B. *J. Am. Chem. Soc.* **1949**, *71*, 1036.

(9) The purity of keto ester 4 greatly affected the course of the reduction. Material of questionable purity required prolonged reaction times for reduction, causing significant decomposition in some runs.

(10) Kanaoka, Y.; Machida, M.; Yonemitsu, O.; Ban, Y. *Chem. Pharm. Bull.* **1965**, *13*, 1065.

(11) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.

(12) Quick, J.; Crelling, J. K. *J. Org. Chem.* **1978**, *43*, 155.

mmol) and Me_3SiCN (83 mL, 660 mmol) under a blanket of nitrogen was added anhydrous ZnI_2 (100 mg). The solution was heated at 90 °C until TLC showed complete disappearance of 2, ca. 15 min. The excess Me_3SiCN was then removed at high vacuum at room temperature, and the resulting $OSiMe_3$ cyanohydrin was used directly without isolation. To a solution of diisopropylamine (101 mL, 720 mmol) in anhydrous ether (2.0 L) cooled to −78 °C under a blanket of nitrogen was added *n*-butyllithium (450 mL, 720 mmol of 1.6 M solution in hexane), and the resulting solution of LDA was stirred 15 min. To the LDA solution was added the above $OSiMe_3$ cyanohydrin as a solution in ether (200 mL), and the resulting orange solution was maintained at −78 °C for 30 min. *tert*-Butyl crotonate[13] (107 g, 750 mmol) in ether (200 mL) was then added dropwise at a rate such that the temperature remained below −70 °C. The resulting solution was stirred at −78 °C for 1 h and then allowed to warm to 0 °C. The etheral solution was extracted with 1 M HCl (5 × 500 mL) and with saturated brine (2 × 500 mL). The aqueous layers were extracted with ether (2 × 500 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give the intermediate crude $OSiMe_3$ cyanohydrin keto ester as an amber oil. The oil was dissolved in ethanol (300 mL) and to the solution was added $KF{\cdot}2H_2O$ (71 g, 750 mmol). The reaction was stirred at room temperature for 30 min, at which time TLC showed complete deprotection. The mixture was partitioned between hexane and water (500 mL each), and the resulting aqueous layer was extracted with hexane (3 × 300 mL). The combined hexane layers were washed with saturated brine (2 × 200 mL), dried over Na_2SO_4, filtered, and evaporated to give 220 g of an amber syrup. Kugelrohr distillation (120 °C, 0.05 mm) from K_2CO_3 gave the keto ester 4 (187 g, 534 mmol, 88%) as a pale green/yellow syrup which crystallized on standing. Recrystallization from petroleum ether afforded white needles: mp 75–76 °C; NMR 7.40 (d, 1 H, J = 9 Hz), 6.90 (d, 1 H, J = 9 Hz), 3.90 (s, 6 H), 2.00–3.80 (m, 4 H), 1.40 (s, 9 H), 1.00–1.40 (m, 9 H); IR 2975, 2940, 1725, 1680, 1585, 1560, 1485, 1455, 1415, 1375, 1365, 1345, 1300, 1265, 1250, 1220, 1150, 1065, 1030, 990; ^{13}C NMR 16.66, 21.88, 21.94, 28.12, 29.94, 38.26, 42.03, 55.69, 60.70, 80.62, 109.30, 123.24, 133.74, 140.86, 149.12, 154.84, 171.84, 207.93; mass spectrum, 350 (M^+), 293, 277, 234, 207, 57. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.55; H, 8.63. Found: C, 68.30; H, 8.81.

5-Isopropyl-6,7-dimethoxy-3-methyl-1-tetralone (7). A solution of keto ester 4 (26.25 g, 75 mmol) in acetic acid (100 mL) and perchloric acid (20 mL) was hydrogenated at 50 psi and 60 °C over 10% Pd–C (3 g). The reaction was monitored by TLC (2% HOAc in 3:1 CH_2Cl_2–ethyl acetate) for disappearance of the transient keto acid, which could be generated by exposing 4 to TFA in dichloromethane. When TLC showed complete conversion, (ca. 3–4 h), the reaction mixture was cooled and filtered through a pad of Celite, and the pad was washed with THF. The combined filtrates were evaporated at high vacuum to a volume of approximately 100 mL. The perchloric acid was neutralized by the addition of sodium acetate (50 g), and the solution was then evaporated to near dryness without excessive heating. The residue was partitioned between ether and water (200 mL each), and the ether layer was then washed with additional water (2 × 100 mL) and with 1 M NaOH (4 × 100 mL). The basic aqueous layers were combined, washed with ether (2 × 50 mL), acidified in the presence of ether (100 mL), and washed with additional ether (4 × 100 mL). The combined ether extracts were washed with saturated brine (2 × 100 mL), dried over Na_2SO_4, filtered, and evaporated to give crude acid 6 (21.0 g) as a light yellow syrup. Last traces of water and acetic acid were removed by reevaporation from toluene. The acid 6 was dissolved in dichloromethane (100 mL), and to it was then added to a solution of polyphosphate ester[10] (PPE, 25 g) in dichloromethane (50 mL). The reaction mixture was stirred at reflux for 30 min, at which time TLC showed conversion to product. The PPE was hydrolyzed by the addition of saturated sodium bicarbonate (150 mL). The layers were separated, and the aqueous layer was extracted with ether (4 × 50 mL). The combined organic layers were washed with water (2 × 100 mL) and saturated brine (2 × 100 mL), dried over Na_2SO_4, filtered, and evaporated to give a solid, which was recrystallized from ether–hexane (1:4) to yield 16.90 g (64.5 mmol, 86%) of tetralone 7: mp 98–99 °C; NMR 7.60 (s, 1 H), 3.95 (s, 6 H), 3.45 (sept, 1 H, J = 7 Hz), 1.90–3.20 (m, 5 H), 1.45 (d, 6 H, J = 7 Hz), 1.20 (d, 3 H); IR 2950, 2920, 1680, 1590, 1480, 1460, 1430, 1410, 1340, 1300, 1260, 1220, 1175, 1140, 1120, 1070, 1030, 980; ^{13}C NMR 21.29, 21.78, 27.99, 30.23, 35.27, 46.36, 55.66, 108.13, 128.54, 135.66, 139.27, 151.72, 153.31, 198.28; mass spectrum, 262 (M^+), 247, 232, 219. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.52; H, 8.69.

5-Isopropyl-6,7-dimethoxy-3-methyl-1-naphthyl Acetate (8). To a solution of tetralone 7 (18.3 g, 70 mmol) in toluene (150 mL) were added isopropenyl acetate (50 mL, 450 mmol) and H_2SO_4 (concentrated, 10 drops). The pale yellow solution was brought to reflux and maintained there for 2 h, at which time TLC showed complete disappearance of 7, indicating conversion to the corresponding enol acetate. The solution was cooled, and to it was added *o*-chloranil (18.1 g, 73.5 mmol). The deep red solution was brought to reflux and maintained there, during which time the color faded slowly. After 1 h, TLC showed complete consumption of the intermediate enol acetate. The solution was cooled, diluted with 2 volumes of ether, and washed with saturated $NaHCO_3$ (5 × 100 mL) and saturated brine (2 × 100 mL). The organic layer was dried, filtered, and evaporated to give a crude brown solid. Filtration through silica gel with CH_2Cl_2 as eluant removed the catechol byproduct. The filtrate was evaporated and the resulting solid was recrystallized from petroleum ether to yield 20.7 g (68.6 mmol, 98%) of acetate 8: mp 123–124 °C; NMR 7.85 (s, 1 H), 7.05 (s, 2 H), 4.00 (sept, 1 H, J = 7 Hz), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.50 (s, 3 H), 2.40 (s, 3 H), 1.50 (d, 6 H, J = 7 Hz); IR 2960, 2940, 1770, 1600, 1475, 1430, 1375, 1275, 1210, 1150, 1020; ^{13}C NMR 21.03, 22.04, 22.14, 26.98, 55.40, 61.12, 98.83, 119.08, 121.85, 123.05, 129.39, 132.70, 135.53, 146.13, 152.37, 169.76; mass spectrum, 302 (M^+), 260, 245, 43. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.25; H, 7.37.

5-Isopropyl-6,7-dimethoxy-3-methyl-1-naphthol (9). To a solution of acetate 8 (18.1 g, 60 mmol) in DME (100 mL) was added $NaBH_4$ (11.34 g, 300 mmol). The resulting suspension was brought to reflux and maintained for 3 h, at which time TLC showed complete conversion. The reaction mixture was cooled, partitioned between pentane and water, and then quenched with concentrated HCl. The resulting aqueous layer was extracted with pentane (3 × 100 mL). The combined pentane layers were washed with 1 M HCl (2 × 100 mL) and saturated brine (2 × 100 mL), dried, filtered, and evaporated to yield 15.0 g (57.6 mmol, 96%) of fine white crystals of 9: mp 133–134 °C (lit.[2d] mp 129–130 °C); NMR 7.60 (s, 2 H), 6.65 (s, 1 H), 6.15 (s, 1 H, exch), 4.00 (sept, 1 H, J = 7 Hz), 3.95 (s, 6 H), 2.45 (s, 3 H), 1.50 (d, 6 H, J = 7 Hz); IR 3460, 2960, 1600, 1465, 1420, 1405, 1335, 1275, 1240, 1195, 1140; mass spectrum, 260 (M^+), 245, 230, 215, 128, 115; ^{13}C NMR 22.07, 26.98, 55.53, 61.15, 99.87, 109.86, 116.51, 120.12, 129.39, 133.06, 135.11, 139.89, 144.80, 150.91. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.60; H, 7.95.

5,5′-Diisopropyl-6,6′,7,7′-tetramethoxy-3,3′-dimethyl-[2,2′-binaphthyl]-1,1′-diol (10). Dimerization of naphthol 9 (2.60 g, 10 mmol) was carried out at 150–215 °C according to the literature[2d] to yield binaphthol 10 (2.46 g, 4.75 mmol, 95%): mp 274–276 °C from hexane–CH_2Cl_2[14] (lit.[2d] mp 271–274 °C from benzene–methanol); NMR 7.82 (s, 2 H), 7.55 (s, 2 H), 5.35 (s, 2 H), 4.10 (s, 6 H), 4.02 (s, 6 H), 3.95 (sept, 2 H, J = 7 Hz), 2.20 (s, 6 H), 1.65 (d, 12 H, J = 7 Hz); IR 3520, 3440, 2960, 1600, 1450, 1420, 1365, 1330, 1245, 1195, 1170, 1145, 1030, 840; mass spectrum, 518 (M^+), 504, 259, 244, 215, 185, 169, 115, 91; ^{13}C NMR 20.74, 22.24, 26.98, 55.53, 61.15, 100.75, 133.39, 117.36, 120.51, 129.26, 132.90, 134.98, 148.63, 149.64, 151.62. Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.11; H, 7.38. Found: C, 73.68; H, 7.38.

Apogossypol Hexamethyl Ether (11). Binaphthol 10 (1.30 g, 2.50 mmol) was dissolved in acetone, and to the solution was added dimethyl sulfate (1.42 mL, 15 mmol) followed by KOH (0.84

(13) *tert*-Butyl crotonate was prepared by reaction of *tert*-butyl alcohol with crotonyl chloride in the presence of dimethylaniline in refluxing ether in 79–84% yield, bp 90 °C (100 mm); prepared from crotonic acid and isobutylene, lit. bp 77–78 °C (50 mm): Pavlov, S.; Bogavac, M.; Arsenijevic, V. *Bull. Soc. Chim. Fr.* **1974**, 2985.

(14) In some runs of more than 10 mmol, significant further oxidation of 10 occurred before conversion of 9 was completed. Extensive manipulation or chromatography of 10 also caused significant loss in yield. Direct methylation of crude 10 to give 11 is preferred.

g of 80%, 12 mmol). The resulting solution was stirred at room temperature until TLC showed disappearance of 10. The solution was evaporated, and the residue was partitioned between CH_2Cl_2 and 1 M HCl (50 mL each). The organic layer was washed with additional 1 M HCl (3 × 50 mL) and saturated brine (2 × 50 mL), dried over Na_2SO_4, filtered, and evaporated to give a solid, which was filtered through silica gel with CH_2Cl_2 as eluant and recrystallized from hexane–dichloromethane to yield 1.19 g (2.18 mmol, 87%): mp 272 °C (lit.[2d] mp 277–279 °C from benzene–methanol); NMR 7.85 (s, 2 H), 7.42 (s, 2 H), 4.05 (sept, 2 H, J = 7 Hz), 3.97 (s, 6 H), 3.92 (s, 6 H), 3.57 (s, 6 H), 2.20 (s, 6 H), 1.55 (d, 12 H, J = 7 Hz); IR 2950, 1595, 1475, 1450, 1410, 1350, 1275, 1235, 1210, 1135, 1025, 1010, 825; ^{13}C NMR 20.00, 22.27, 27.05, 55.50, 60.57, 100.71, 120.51, 124.84, 126.56, 128.87, 132.90, 135.21, 152.05, 152.92. Anal. Calcd for $C_{34}H_{42}O_6$: C, 74.70; H, 7.74. Found: C, 74.56; H, 7.88.

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Ring-Closure Reactions. 18.[1] Application of the Malonic Ester Synthesis to the Preparation of Many-Membered Carbocyclic Rings

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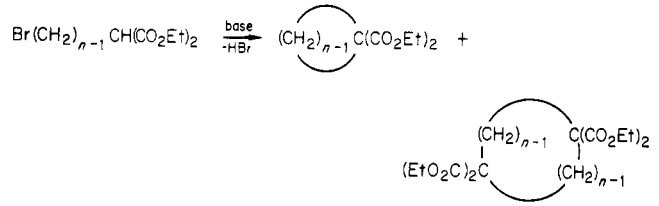
Alkylation of malonic ester derivatives with alkyl halides is a very well-known method for C–C bond formation. The intramolecular version of this reaction has been used for the synthesis of small and common carbocyclic rings.[2] Herein we describe a modification of the intramolecular malonic ester synthesis which permits the cyclization of long-chain diethyl ω-bromoalkylmalonates to many-membered 1,1-bis(ethoxycarbonyl)cycloalkanes under high dilution conditions.



The critical parameter to be adjusted in a high-dilution cyclization is the rate of feed of the bifunctional reactant into the reaction medium.[3] This is because of the necessity of achieving a stationary concentration of the reactant low enough as to favor the intramolecular reaction. The usefulness of many macrocyclization procedures is often hampered by the exceedingly low rates of feed required to fulfill the above condition, which result in very long addition times and large amounts of solvent to cyclize a synthetically significant amount of material. Since, other things being equal, the rate of feed has to be lower, the lower the rate of the reaction at hand,[3] it is of considerable advantage to carry out a cyclization reaction under conditions (solvent, temperature, catalyst, etc.) corresponding to the highest reactivity of the functional groups. Accordingly, cyclization was carried out in Me_2SO, which, as shown by literature data,[4] is the best of several tested solvents for the alkylation of the alkali derivatives of alkylmalonic esters with alkyl bromides. The base used was EtOK·18-crown-6 (1:1 mole ratio). Replacement of Na^+ for K^+, as well as omission of 18-crown-6, resulted in poorer yields. For instance, the yield of the 12-membered ring dropped from 21% to 13% with EtONa·18-crown-6 and to 3% with EtOK alone. This clearly indicates that dissociate enolate ions improve the yield. By virtue of the above solvent–base combination, the high-dilution condition could be attained with a relatively high rate of feed of the reactants into the reaction medium, namely, 6×10^{-7} mol L^{-1} s^{-1}. This permitted the total addition time to be kept conveniently within 3 to 4 h.

Table I. Cyclization of $Br(CH_2)_{n-1}CH(CO_2Et)_2$ with EtOK·18-Crown-6 in Me_2SO at 80 °C under High-Dilution Conditions

monomeric rings, n	6	7	8	9	10	11	12	13	17	21
isolated yield, %[a]		68	22				32[b]	52	62	55
GLC yield, %	72	70	22	3[c]	0.1[c]	1[c]	34	52		
dimeric rings, $2n$	12	14	16	18	20	22	24	26	34	42
isolated yield, %[d]			30	22	10	50	19	9		

[a] From column chromatography. All new compounds gave satisfactory analytical data (maximum deviation ±0.24 for C; ±0.20 for H). [b] mp 115–117 °C after sublimation in vacuo. All the other isolated monomeric rings behave as liquids at room temperature. It is known (Dale, J. *J. Chem. Soc.* **1963**, 93) that a series of ring compounds may show very irregular melting point patterns often characterized by large differences between even- and odd-membered rings, with higher melting points for the even-membered ones. Thus, the 12-membered ring being the only one to behave as a solid is not surprising, since the larger-than-12-membered rings are all odd membered. [c] Characterized by GLC–MS analysis. [d] From column chromatography. The dimeric rings (ring size in parentheses) had the following melting points (°C): (16) 128–130 from MeOH; (18) 128–130 from MeOH; (20) 100–102 from MeOH; (22) 111–112 from low-boiling petroleum ether; (24) 106–107 from low-boiling petroleum ether; (26) 110–113 from ligroin.

One further advantage of Me_2SO is that in this solvent the acid–base reaction between the malonic ester derivatives and EtO^- is virtually quantitative even in very dilute solutions,[5] so that if exactly equivalent amounts of base and bifunctional substrate are allowed to flow into the reaction medium, cyclization can take place in the virtual absence of the undesirable side reaction between EtO^- and the CH_2Br end. This aim was achieved by the use of a pair of motor-driven syringes which, also, allowed use of exactly the same rate of feed for all substrates.

The cyclization was successful in producing fairly good yields of common and large-sized carbocyclic rings (Table I). The medium rings were obtained in distinctly lower yields and were accompanied by significant amounts of the dimeric ring products. Contrary to expectation, worse results were obtained on prolonging the addition time to

(1) Part 17: Dalla Cort, A; Mandolini, L.; Masci, B. *J. Org. Chem.* **1980**, *45*, 3923.
(2) (a) Perkin, W. H. *J. Chem. Soc.* **1885**, *47*, 801. (b) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 67. (c) Birch, S. F.; Dean, R. A.; Whitehead, E. *J. Org. Chem.* **1954**, *19*, 1449.
(3) Galli, C.; Mandolini, L. *Gazz. Chim. Ital.* **1975**, *105*, 367.
(4) (a) Zaugg, H. E.; Schaefer, A. D. *J. Am. Chem. Soc.* **1965**, *87*, 1857. (b) Zaugg, H. E.; Horron, B. W.; Borgward, S. *J. Am. Chem. Soc.* **1960**, *82*, 2895. (c) Zaugg, H. E. *J. Am. Chem. Soc.* **1961**, *83*, 837. (d) Deschamps, E.; Ginsburg, H.; Le Ny, G.; Nee, G.; Tchoubar, B. *Nouv. J. Chim.* **1980**, *4*, 261.

0022-3263/81/1946-3127$01.25/0