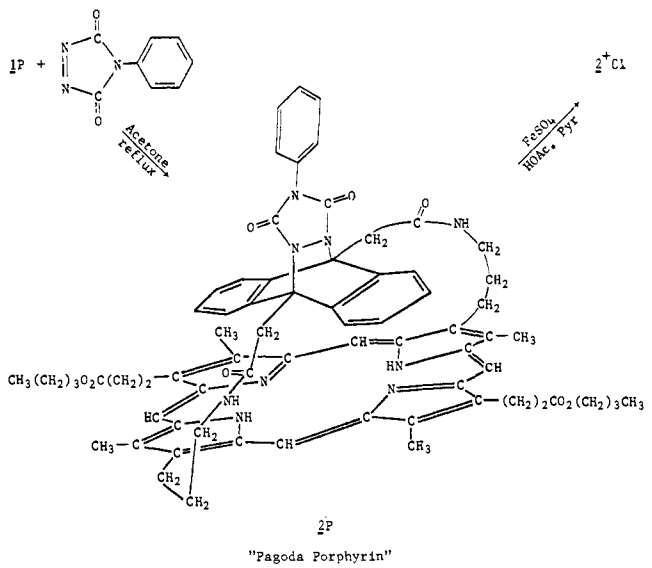
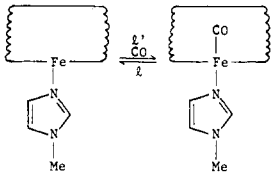
Scheme II



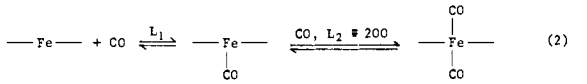
steric hindrance with the second aromatic group. To reduce the flexibility of the cyclophane ring, we have used two strategies. First, by using anthracene connected at the 9,10 positions, the tilting of this ring is severely limited. Secondly, by performing a Diels-Alder addition to the anthracene-porphyrin cyclophane, an even further restriction and tighter pocket is achieved. The syntheses are outlined in Schemes I and II.[14]

Properties of Anthracene-Heme [6.6]Cyclophane (1). The first striking property of this heme is its behavior toward 1-methylimidazole. At 1 M 1-methylimidazole in methylene chloride, the spectrum of this heme shows a five-coordinated spectrum at 418 and 543 nm, previously observed with "capped heme" by Baldwin et al.[17] Under these conditions the binding constant for a second imidazole would be $\sim 10^4$ M^{-1}.[18a]

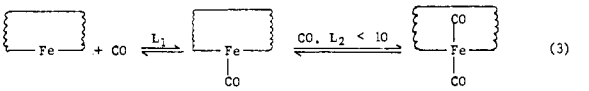


(1)

A more pertinent steric effect of the anthracene ring was demonstrated by preparing the CO complex in dry benzene by the method of Rougee and Brault.[18b] At 1 atm of CO pressure the spectrum showed a single Soret band at 394 nm corresponding to pure monocarbonyl heme. Under these conditions deuteroheme was reported to be ~50% monocarbonyl and 50% dicarbonyl heme.[18b] Therefore, the anthracene has greatly reduced the affinity of the second CO.



(2)



(3)

Additional evidence for distal side steric effects comes from kinetic measurements. Kinetic measurements in methylene chloride containing 0.2 M 1-methylimidazole were complex but clearly demonstrated that the second-order rate constants, l', for CO combination according to eq 1 were $<10^4$ M^{-1} s^{-1} for the anthracene heme cyclophane **1** and $<10^3$ M^{-1} s^{-1} for the "pagoda" heme **2.** These compare with 10^7 M^{-1} s^{-1} for chelated hemes without the steric effect.[7c] These drastic reductions in CO association rates can be attributed to the steric hindrance in the synthetic heme pocket. We have previously shown that solvent effects are not important in heme-CO kinetics or equilibria.[7a]

Further studies of steric hindrance to CO, CN^-, and O_2 binding are in progress.

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(14) NMR and UV-visible spectra are consistent with the cyclophane porphyrin structure **1P** shown. Both the anthracene and porphyrin UV-visible and NMR spectra appear in the cyclophane. The aromatic proton resonances are shifted upfield by 2 ppm upon converting the anthracene into the cyclophane as would be expected from the porphyrin ring-current effects. The general synthetic scheme follows that employed by Chang[15] and the anthracene diacetic acid was prepared as described by Kretov and Litvinov.[16] The symbols **1P, 1, 1^+Cl^-** refer to the free porphyrin, the heme, and the hemin chloride, respectively.[9]
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Macrolide Antibiotics. 1. Total Synthesis of the Prelog-Djerassi Lactone and Methynolide

Sir:

Efforts directed toward the total synthesis of the macrolide antibiotic methymycin[1] have evolved around the Prelog-Djerassi lactone **1**,[2] a key degradation product of methymycin retaining the original four chiral centers present in the C(1)-C(7) segment of the aglycone methynolide **2.** Since the first synthesis of (±)-**1** by Masamune[3] which was employed in the only total synthesis of methymycin recorded to date,[4] two additional syntheses of (±)-**1** have appeared.[5] In this communication we report our work in this area which has resulted in a total synthesis of methynolide (**2**). In addition, we record

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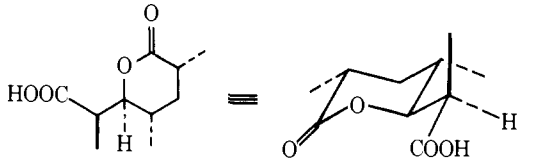
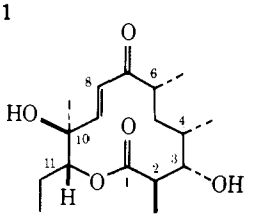


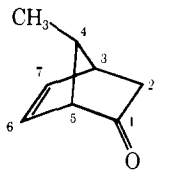
1



2

an efficient synthesis of the Prelog-Djerassi lactone in both racemic and optically active forms.

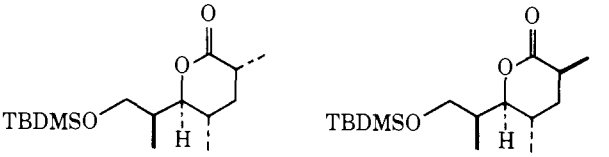
Our strategy centered around the bicyclo[2.2.1]heptenone **3**[6] which possesses, in masked form, the complete carbon



3

framework of the Prelog-Djerassi lactone and the seven carbon atoms of the C(1)-C(7) structural fragment of methymycin. Alkylation of bicyclo[2.2.1]heptenone **3** provided (67%) volatile ketone **4** as the sole product. NMR analysis (250 MHz) of **4** revealed the C(2) endo proton as a quartet (J = 7.0 Hz) centered at δ 1.94 in complete agreement with the assigned structure.[8] Baeyer-Villiger oxidation of ketone **4** afforded a lactone (IR (film) 1720 cm^{-1}) which smoothly rearranged to bicyclic lactone **5** (Scheme I) (IR (film) 1760 cm^{-1}). Reduction of **5** gave an olefinic diol which when subjected to hydrogenation provided the crystalline diol **6,** mp 53-54 °C. Protection of the primary hydroxyl as its *tert*-butyldimethylsilyl ether[9] and subsequent Collins oxidation of the resultant cyclopentanol afforded cyclopentanone **7** (IR (CCl_4) 1740 cm^{-1}).

Methylation of lactone **8** obtained via Baeyer-Villiger oxidation of **7** provided a 1:1 mixture of the desired alkylated lactone **9a** (mp 34-35 °C; R_f 0.32 (hexane-ether, 4:1)) and the unwanted isomer **9b** (R_f 0.36). Treatment of a THF solution of the 1:1 mixture of **9a** and **9b** with LDA at −78 °C



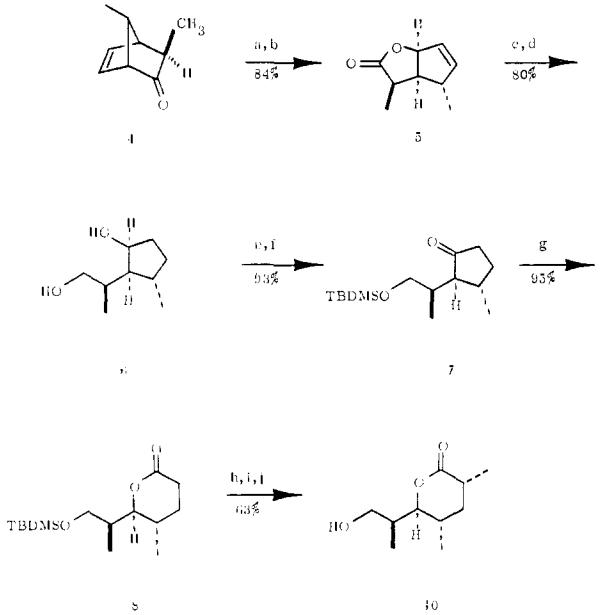
9a **9b**

TBDMS = t-Bu(Me)$_2$Si

followed by kinetic protonation of the lactone enolate gave (85% overall) a 3.5:1 ratio of **9a** and **9b,** respectively, which were separated by chromatography. Desilylation of **9a** afforded hydroxylactone **10** as a crystalline substance, mp 49-50 °C. Oxidation of **10** with Jones reagent gave crystalline racemic Prelog-Djerassi lactone **1** (82%), mp 113-114 °C, identical in all respects (NMR, IR, mass spectrum, melting point, mixture melting point) with an authentic sample of racemic **1.** Optically pure Prelog-Djerassi lactone (**1**), mp 123.5-125.0 °C, $[\alpha]^{25}_D$ +38.7° (c 1.90, $CHCl_3$) (lit.[2a,10] mp 126-128 °C, $[\alpha]_D$ +38° ($CHCl_3$)), was prepared from optically pure bicyclo[2.2.1]heptenone (**3**),[11] $[\alpha]^{25}_D$ −726.3° (c 1.61, $CHCl_3$), using the synthetic sequence described above.[13]

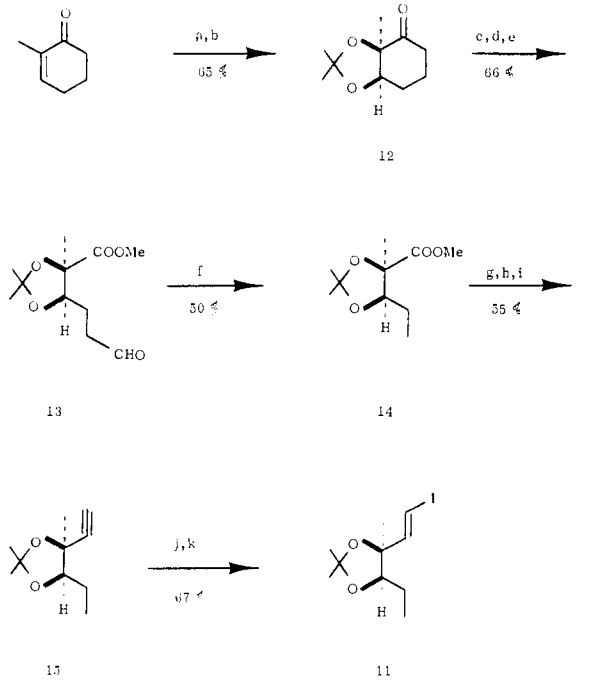
Having constructed the C(1)-C(7) fragment **10,** we focussed our attention on the synthesis of the C(8)-C(11) fragment **11** (Scheme II). Hydroxylation[14] of the conjugated double bond of 2-methylcyclohexenone provided the corresponding diol which was smoothly converted into acetonide **12.**

Scheme I[a]



[a] (a) MCPBA, $NaHCO_3$, CH_2Cl_2, ~5 °C, 23 h; (b) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C; (c) $LiAlH_4$, Et_2O, −20 °C, 1.5 h; (d) H_2, EtOAc, PtO_2; (e) t-Bu(Me)$_2$SiCl, DMF, imidazole, −10 °C; (f) $CrO_3 \cdot 2py$, 0 °C, 15 min; (g) MCPBA, $NaHCO_3$, CH_2Cl_2, 5 °C (14 h) → 25 °C; (h) LDA, THF, HMPA, MeI, −78 °C; (i) LDA, THF, −78 °C, 10% citric acid; (j) CH_3OH, TsOH, 5 °C, 12 h.

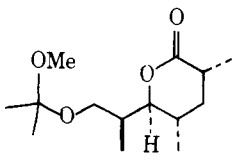
Scheme II[a]



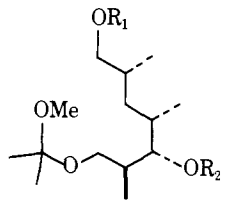
[a] (a) OsO_4 (0.34 equiv), $Ba(ClO_3)_2$ (1.1 equiv), aqueous THF, −10 °C; (b) acetone, $CuSO_4$, TsOH; (c) LDA, THF, Ac_2O, −20 °C; (d) O_3, CH_2Cl_2, −78 °C, Me_2S; (e) CH_2N_2; (f) $[(C_6H_5)_3P]_3RhCl$, CH_2Cl_2; (g) i-Bu_2AlH, $PhCH_3$, −78 °C; (h) CBr_4, $(C_6H_5)_3P$, CH_2Cl_2; (i) BuLi (2.0 equiv), THF, −78 °C; (j) $Cp_2Zr(H)Cl$ (1.0 equiv), PhH, 3 h; (k) I_2, THF, 30 min.

Enol acetate formation followed by ozonolysis and esterification generated aldehyde **13** which was deformylated. Transformation of ester **14** into terminal acetylene **15** was achieved via a three-step sequence[15] as illustrated in Scheme II. Hydrozirconation[16] of **15** using dicyclopentadienylchlorohydridozirconium (1.0 equiv) in benzene (3 h) followed by iodination (I_2, THF, 30 min) provided in 67% yield, as the sole product, pure *trans*-vinyl iodide **11**: NMR (CCl_4) δ 6.30 (AB q, 2 H, J = 14.0 Hz, $\Delta\nu_{AB}$ = 9.6 Hz).

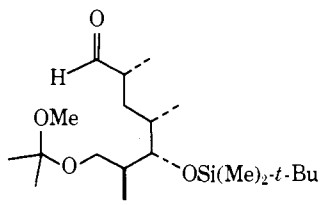
With the C(8)-C(11) segment of methynolide available, we concentrated our efforts on construction of the complete carbon framework of methynolide (**2**). (±)-Alcohol **10** was converted (72%) into **16**, mp 41-42 °C, by treatment with methoxy-



16

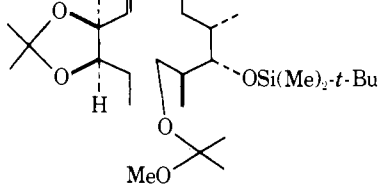


17, R_1 = COPh; R_2 = H
18, R_1 = H; R_2 = Si(Me)$_2$-*t*-Bu



19

propene (2.0 equiv)[17] in methylene chloride containing a catalytic amount of pyridinium *p*-toluenesulfonate.[18] Reduction ($LiAlH_4$, THF) of lactone **16** followed by selective monobenzoylation (PhCOCl, pyr, CH_2Cl_2, −20 °C) provided al-



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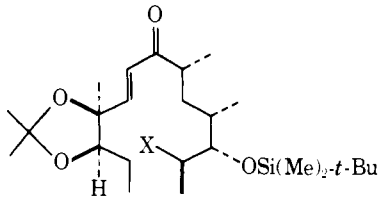
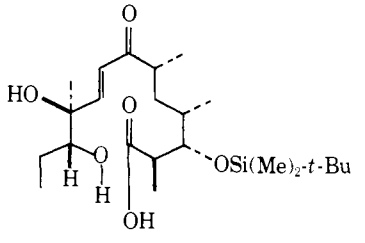


21, X = CH_2OH
22, X = COOH



23

cohol **17** in 87% overall yield. Silylation of **17** and subsequent hydrolysis (5% KOH, MeOH) gave primary alcohol **18**. Collins oxidation of **18** (0 °C, 25 min) afforded in 90% yield aldehyde **19** which was immediately treated with the *trans*-vinyllithium reagent obtained by lithiation of *trans*-vinyl iodide **11** (BuLi, THF, −78 °C). The resulting mixture of diastereomers **20** (74% overall yield from **18**) was submitted to oxidation (MnO_2, PhH) and cleavage (MeOH, TsOH, 0 °C, 5 min) of the labile *O*-methoxyisopropyl group, giving rise to alcohol **21** (a 1:1 mixture of diastereoisomers) in 85% yield. Jones oxidation of **21** (−10 °C, 40 min) afforded a 90% yield of the seco acid derivative **22** which was subjected to 1 N HCl-THF (1:1). Pure seco acid **23** was separated from the unwanted diastereomer by preparative TLC using $CHCl_3$-EtOH-HOAc (20:1:0.1). The NMR spectrum of **23** was in accord with the NMR spectrum of **23** obtained from Professor Masamune. The conversion of seco acid **23** into methynolide on a previous occasion constitutes a total synthesis of aglycone **2**.[4]

Acknowledgment. We are grateful to Professor S. Masamune for supplying us with a sample of synthetic racemic **1** as well as spectra of **1** and seco acid **23**. We thank Professor P. McCurry for providing us with a 250-MHz NMR spectrum of (±)-**1**. This investigation was supported in part by a grant from the National Institutes of Health, the National Institutes of Health NMR Facility for Biomedical Studies, and G. D. Searle & Co. We thank Mr. George Majetich and Mr. Robert Bittner for recording the 250-MHz NMR spectra.

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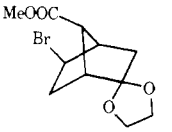
(6) Bicyclo[2.2.1]heptenone **3** was prepared in ~80% overall yield in a straightforward fashion from the known racemic bicyclo[2.2.1]heptane derivative i[7] via a six-step sequence: (1) $LiAlH_4$, Et_2O, 0 °C; (2) DBU, tol-



i

uene, reflux; (3) TsCl, pyr; (4) NaI, methyl ethyl ketone, 80 °C; (5) $LiAlH_4$, THF, reflux; (6) 10% HCl, THF.
(7) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.
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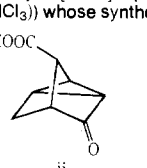
(10) The sample of "natural" 1 obtained by Professor Prelog had mp 124-125 °C, $[\alpha]_D$ +33° (*c* 0.797, $CHCl_3$).[2b]
(11) Bicyclo[2.2.1]heptenone **3** ($[\alpha]^{25}_D$ −726.3° (*c* 1.61, $CHCl_3$)) was prepared as described above from the bicyclo[2.2.1]heptane derivative i (mp 40-41 °C, $[\alpha]^{25}_D$ −1.4° (*c* 2.0, $CHCl_3$)) whose synthesis from cyclopropyl keto



ii

acid ii (mp 137-138 °C, $[\alpha]^{25}_D$ +74° (*c* 1.00, CH_3OH))[12] has previously been described.[7]
(12) Bindra, J. S.; Grodski, A.; Schaaf, T. K.; Corey, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 7522.
(13) The intermediates in the optically active series possessed the following physical constants: **4**, $[\alpha]^{25}_D$ −706.7° (*c* 0.77, $CHCl_3$); **5**, $[\alpha]^{25}_D$ +202.9° (*c* 1.34, $CHCl_3$); **6**, $[\alpha]^{25}_D$ +181.6° (*c* 0.37, $CHCl_3$); **7**, $[\alpha]^{25}_D$ −59.3° (*c* 2.6, $CHCl_3$); **8**, $[\alpha]^{25}_D$ +62.0° (*c* 2.0, $CHCl_3$); **9a**, $[\alpha]^{25}_D$ +47.3° (*c* 2.7, $CHCl_3$); **10**, mp 66-67 °C, $[\alpha]^{25}_D$ +50.0° (*c* 0.9, $CHCl_3$).
(14) Cf.: Pláha, L.; Weichet, J.; Zvâcek, J.; Smolik, S.; Kakâc, B. *Collect. Czech.*

Chem. Commun. **1960**, *25*, 237. Kende, A. S.; Bentley, T. J.; Moder, R. A.; Rldge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332.
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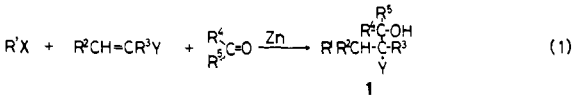
Received March 30, 1979

One-Step Joining Reaction of Thiolate Anions, Activated Olefins, and Carbonyl Compounds

Sir:

Conjugate addition of organometallic reagents to α,β-unsaturated compounds followed by trapping of the resulting anionic intermediates with nucleophiles has been accepted as a versatile tool in organic synthesis,[1] and we have previously reported a zinc-promoted one-step joining reaction of alkyl halides, activated olefins, and carbonyl compounds[1a] (eq 1).



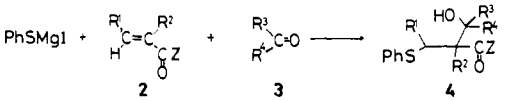
(1)

1

X = halogen
Y = electron-withdrawing group

Concerning these reactions, however, further chemical modification of the group R^1 starting from the products **1** is not necessarily possible.

In the present study, we have found a new one-step joining reaction (eq 2) in which metal thiolates[2] are used as the organometallic reagents, and hence the products **4** have a wide potential in organic synthesis since the thiolate group can easily be eliminated by a variety of methods.[3] The results are shown in Table I.

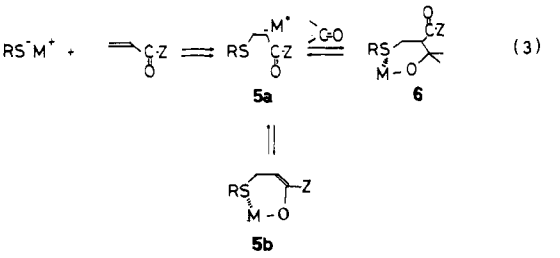


(2)

2 3 4

Z = alkyl or alkoxy group

In this joining reaction, the nature of solvent and the counterion (M^+) of the thiolate anion play important roles in the determination of the reaction pathway (eq 3).



(3)

5a 6 5b

When M^+ is Li^+ or Na^+ and the reaction is carried out in polar solvents such as DMF or acetonitrile, the reaction stops with **5a,b.**[4] The use of MgI^+ as M^+ and nonpolar solvent such as ether and hexane is essential to achieve this joining reaction, since the intermediate **6** can become more stable under these conditions,[5] although the use of Na^+ as M^+ has been reported in a similar stepwise joining reaction in which the second step is the irreversible Wittig-Horner reaction.[6]

This new reaction is characterized by (1) mild reaction conditions, (2) high yields, (3) reasonably wide variety of the compounds **2** and **3**, and (4) high potentiality of the products **4** in organic synthesis as exemplified in Schemes I-III.[7] Scheme II shows a new synthetic route to α-methylene-γ-butyrolactones.[10]

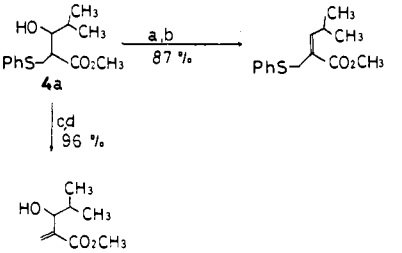
A typical experimental procedure is as follows. To a solution of phenylthiomagnesium iodide[12] (20 mmol) in hexane (20

Table I. One-Step Joining Reaction of Thiolate Anions, Activated Olefins, and Carbonyl Compounds

Activated Olefins (2)	Carbonyl Compounds R^3COR^4 (3)	Products[a,b] (4)	Isolated Yield (%)
2a, $R^1=R^2=H$, Z=OMe	**3a**, R^3=i-Pr, $R^4=H$	**4a**,	96
2a	**3b**, R^3=Ph, $R^4=H$	**4b**,	95
2a	**3c**, R^3=2-furyl, $R^4=H$	**4c**,	87
2a	**3d**, $R^3=R^4=-CH_3$	**4d**,	89
2a	**3e**, $R^3=R^4=-(CH_2)_5-$	**4e**,	72
2b, $R^1=H$, $R^2=CH_3$, Z=OMe	**3a**	**4f**,	97
2b	**3c**	**4g**,	92
2b	**3d**	**4h**,	95
2c, $R^1=CH_3$, $R^2=H$, Z=OMe	**3a**	**4i**,	90
2c	**3f**, R^3=n-C_6H_{13}, $R^4=H$	**4j**,	83
2c	**3d**	**4k**,	92
2d, $R^1=R^2=H$, $Z=CH_3$	**3a**	**4l**,	100
2e, 	**3a**	**4m**, 	90

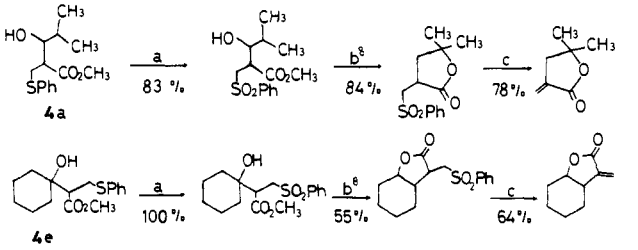
[a] Spectroscopic and elemental analyses of all products were satisfactory for assigned structures. [b] A mixture of diastereomers.

Scheme I[a]



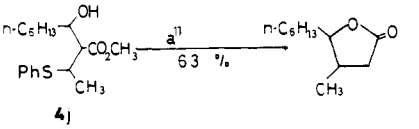
[a] (a) CH_3SO_2Cl, pyridine, room temperature. (b) reflux in pyridine; (c) $NaIO_4$, MeOH–H_2O–benzene (1:1:0.05); (d) reflux in toluene.

Scheme II[a]



[a] (a) *m*-Cl-PBA; (b) concentrated H_2SO_4, room temperature; (c) Na_2CO_3 in DMF, room temperature.

Scheme III[a]



[a] (a) Electroreduction.

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