stitution on either of the α and β-positions.

Of particular significance is that our procedure renders the carbonyl functions under protection as alkenyl thioethers until the final stage, allowing further C_3 homologation. Indeed, the synthesis of one 4,7-diketoester was achieved as illustrated in Scheme I.[10]

We suppose that the repeated $C_1 + C_2$ elongation will proceed without difficulty to provide higher homologs. Therefore, the strategy disclosed herein is promising and practical to afford polycarbonyl compounds bearing the repeating β-carbonyl C_3 units.

Acknowledgment. This work was supported in part by Grant-in-Aid for Scientific Research on Priority Area, "Advanced Molecular Conversion", The Ministry of Education, Science, and Culture, Japan.

Supplementary Material Available: NMR and spectral data for compounds in this paper (8 pages). Ordering information is given on any current masthead page.

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Molecular Yardsticks. Synthesis of Extended Equilibrium Transfer Alkylating Cross-link Reagents and Their Use in the Formation of Macrocycles

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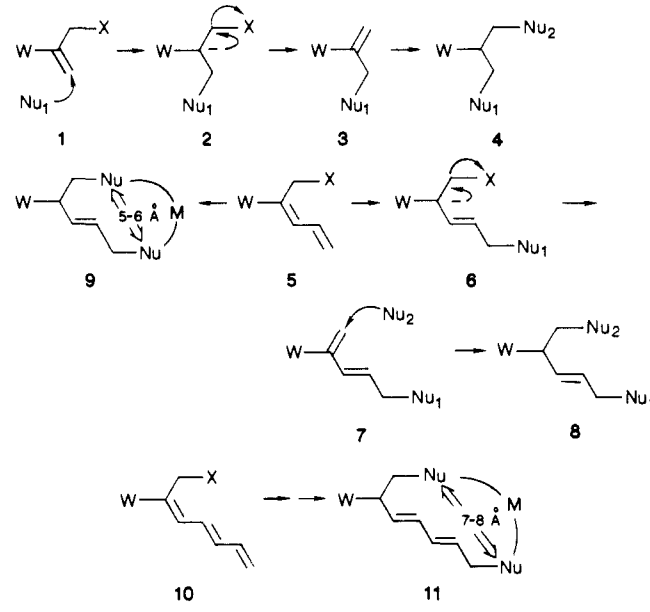
Received April 21, 1988

Some years ago our group introduced reagents [**1**] for sequential alkylation through consecutive Michael reactions [**1** → **4**].[1] Since that time, a variety of different Michael activating groups [W = -CO_2R, -COR, -NO_2, -CN, -SO_2-R, O_2N-C_6H_4-] and leaving groups [X = -Cl, -Br, -$N(CH_3)_3^+$, -OCOC$(CH_3)_3$] have been explored for this sequence of reactions. Seebach and Knochel,[2] Stetter,[3] Cromwell,[4] Doomes,[5] Fuchs,[6] Peters and van Bekkem,[7] and others have made beautiful contributions to this chemistry. The technique was extended by us to the cross-linking of proteins.[8] We have sought an efficient entry to structurally and mechanistically similar molecules having high Michael reactivity, suppressed direct displacement chemistry, and extended conjugation [for example **5** or **10**]. The extended structures are "yardsticks", able to bridge incrementally longer distances between nucleophilic groups in either complex proteins or simple frameworks. This cross-linking concept can be extrapolated to the chemical synthesis of interesting macrocyclic rings [**9** and **11**].

Scheme I



The competition between direct displacement and Michael addition in the first step of the sequence depends upon the attacking nucleophile [Nu1], activation [W] of the double bond, and character of the leaving group [X]. Keto hydroxyethylsulfonylmethyldiene and polyene structures [**12–21**, Scheme II] were chosen as meeting the desired criteria. Such molecules contain an α-methylene with a leaving group (X = SO_2-R) not prone to direct displacement combined with a strong activating group for the Michael reaction (W = ketone) that could be easily reduced in aqueous media. This last criterion was required so that in protein systems the equilibrium transfer process can be arrested if necessary and the linked sites can be identified.[8] The hydroxyl group was appended to give a chelating arm for synthetic reasons and for providing attachment sites for water solubilizing groups in protein cross-link studies. The nitro function was appended to give a site for eventual attachment of probes for protein studies. Various degrees of conjugation [**12**, **18**, **21**] and of double bond substitution [**13–17**, **18–20**] were prepared to determine their effects on the primary site of Michael addition.[9] These molecules are constructed in a remarkably efficient way by a chelated titanium-mediated aldol–dehydration sequence.

Adding $TiCl_4$ and diisopropylethylamine[10,11] at −40 °C to β-((2-hydroxyethyl)thio)-*m*-nitropropiophenone [**30**], mp 58.0–58.5 °C (prepared from the corresponding Mannich salt[12]), in THF gave a chelated complex **31** which condensed with aldehydes[13] giving essentially quantitative yields of the hydroxyethylthiomethylenones [**32**, R = H, CH_3, C_6H_5, CH=CH_2, CH=CH-C_6H_5, etc.] with a 10–15:1 *Z*/*E* selectivity of the major isomer as determined by NMR analysis of the crude product mixture. Oxidation of the olefinic sulfides by *m*-CPBA in chloroform at 0 °C for 5 min gave the corresponding sulfones in good isolated yields (60–90%). The stereochemistry about the newly formed double bonds for these ((2-hydroxyethyl)sulfonyl)methyl dienes, trienes, and tetraenones [**12–21**] has been substantiated to be of

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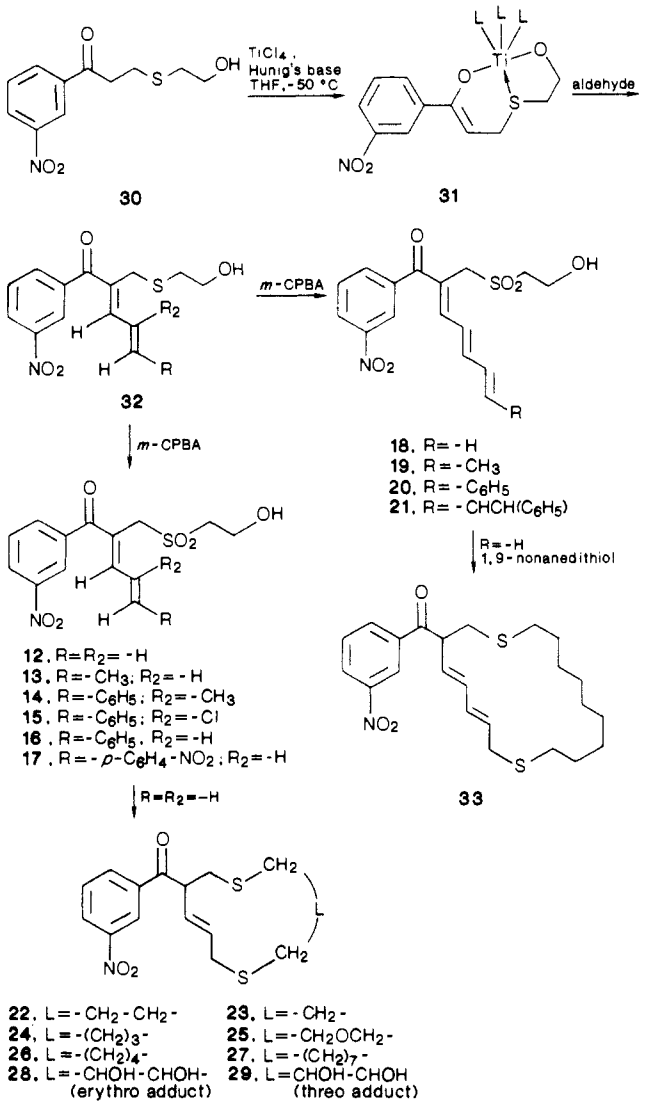
Scheme II



30 31 32 33

18. R=-H
19. R=-CH_3
20. R=-C_6H_5
21. R=-CHCH(C_6H_5)

12. R=R_2=-H
13. R=-CH_3; R_2=-H
14. R=-C_6H_5; R_2=-CH_3
15. R=-C_6H_5; R_2=-Cl
16. R=-C_6H_5, R_2=-H
17. R=-p-C_6H_4-NO_2; R_2=-H

22. L=-CH_2-CH_2-
23. L=-CH_2-
24. L=-$(CH_2)_3$-
25. L=-CH_2OCH_2-
26. L=-$(CH_2)_4$-
27. L=-$(CH_2)_7$-
28. L=-CHOH-CHOH- (erythro adduct)
29. L=CHOH-CHOH (threo adduct)

the *Z* configuration through X-ray crystallographic study of the cinnamaldehyde condensation and oxidation product, 2-[[(2-hydroxyethyl)sulfonyl]methyl]-5-phenyl-*m*-nitro-2(*Z*),4(*E*)-pentadienophenone [**16**], mp 135.5–137 °C, and NMR comparisons with that material.[14]

Simultaneous addition of 1,4-butanedithiol with diisopropylethylamine and 2-[[(2-hydroxyethyl)sulfonyl]methyl]-*m*-nitro-2(*Z*),4(*E*)-pentadienophenone [**12**], mp 133.5–135 °C, to a methanol solution containing a trace of hydroquinone at −40 °C afforded the 11-membered macrocyclic structure, 3-(*m*-nitrobenzoyl)-1,7-dithia-*trans*-4-cycloundecene [**22**], mp 109–111 °C, as the only product (45% yield, crystallized). The structure was confirmed by X-ray crystallographic analysis [Figure 1]. In the absence of the hydroquinone radical trap, a certain amount of the product is transformed to an isomer, presumed to have the cis configuration. Analogous results were obtained with the combination of **12** with 1,3-propanedithiol (forming a 10-membered ring, **23**, oil), with 1,5-pentanedithiol or dimercaptoethyl ether (yielding 12-membered rings, **24**; mp 97.5–105 °C; **25**, mp 95–96.5 °C; complexes with hydroquinone and chloroform), with 1,6-hexanedithiol (forming a 13-membered ring, 3-(*m*-nitrobenzoyl)-1,7-dithia-4(*E*)-cyclotridecene [**26**], mp 126–127.5 °C), with 1,9-nonanedithiol (to form a 16-membered ring, **27**, oil), and

(14) Carbon–hydrogen analyses, proton and carbon NMR, IR, and mass spectral data have been obtained for all new compounds for which data are given and are consistent with the structures proposed. The X-ray crystallographic work was accomplished by Dr. William Butler and Myoung Soo Lah of the University of Michigan Chemistry Department Crystallography Unit.

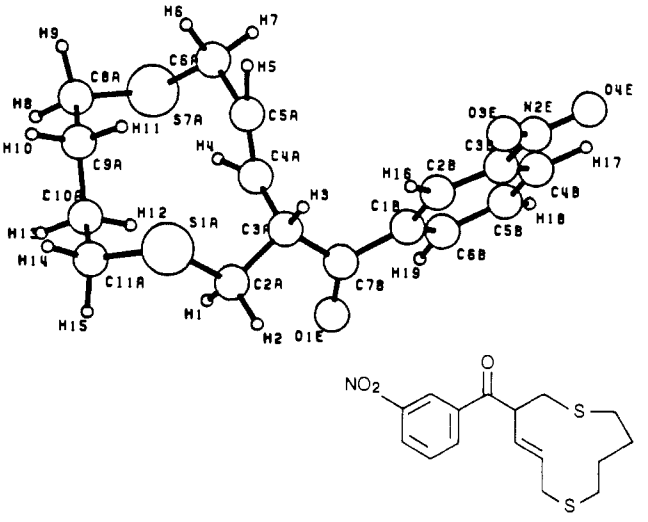


Figure 1.

with dithioerythritol and dithiothreitol to form, in each example, single crystalline stereoisomers of the functionalized, 11-membered ring structures **28**, mp 164–166.5 °C, and **29**, mp 178–179 °C. 1,9-Nonanedithiol has also been added to the ((hydroxyethyl)-sulfonyl)methyl trienone **18**, mp 126–127 °C, giving the *trans,-trans*(*E,E*) 18-membered ring 3-(*m*-nitrobenzoyl)-1,9-dithia-*trans*-4-*trans*-6-cyclooctadecadiene, mp 100.75–102 °C [**33**]. Preliminary results indicate that amines, diamines, and carbon nucleophiles such as malonic ester and Meldrums acid also add in similar double fashion to these agents. More substituted reagents (i.e., **13**, **15**) react similarly. The pathway appears to be very general.

In these examples, the addition of a molecule having two (or more) nucleophilic sites to such extended reagent(s) [**5**] results in Michael addition followed by elimination of the sulfone group [**6** → **7**]. This leads to an intermediate [**7**] having a newly created, cross-conjugated Michael acceptor double bond *more reactive* than those in the starting reagent. Only then can the second Michael reaction occur [**7** → **8**]. In the addition of simple model dithiols, this format favors intramolecular cross-linking with formation of macrocyclic rings [**9**]. Intermolecular addition and polymerization by reaction with another molecule more conjugated and thus less reactive is less competitive even though starting alkylating molecules [**5**] may be present in relatively high concentration. We believe the sequential alkylation to form macrocyclic rings does not solely depend upon high dilution techniques or ring size as long as the bridging groups of the adding structure are long enough to reach the ends of the conjugated system and the rate of the second Michael addition is fast compared to the first addition. However, reverse Michael reactions and radical chain processes also must be suppressed.

In addition to protein cross-linking studies, we anticipate the use of the reagents and technique in the construction of highly functionalized macrocyclics, catenanes, and crown ether and molecular recognition type molecules. The application to the determination of distances by the linking of nucleophilic residues on less flexible synthetic models is underway. Reports on the successful use of these molecular yardsticks in the cross-linking of certain peptides, proteins, and protein aggregates are in preparation.

Acknowledgment. We acknowledge and appreciate the support of the National Science Foundation, Synthetic Organic and Natural Products Division, Grant CHE8421137 AO2, NSF Instrumentation Program and to the Colgate Palmolive Research Laboratories for summer research fellowships.

Supplementary Material Available: NMR spectral data, NMR spectra, a structural representation, and a listing of each compound (88 pages). Ordering information is given on any current masthead page.