DIHYDROTHIOPYRANS IN COMPLEX TOTAL SYNTHESIS

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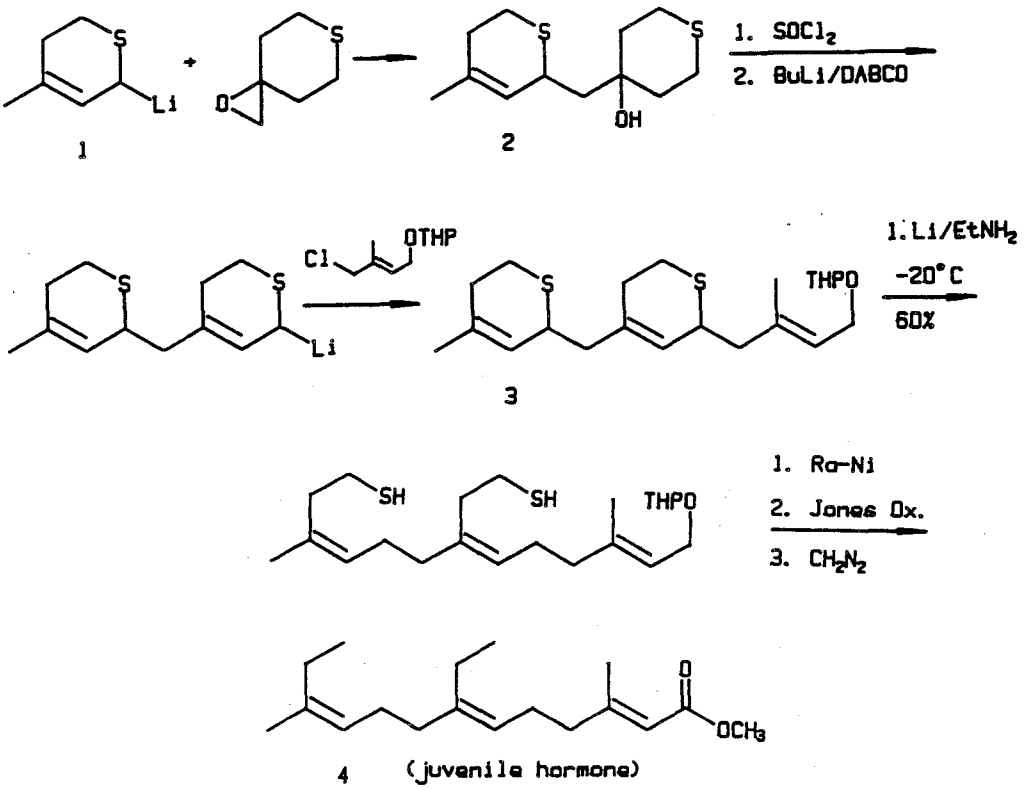
Until recently, dihydrothiopyrans have played only an occasional role in natural product synthesis. In part, this is for reasons which are common to virtually all synthetic uses of organosulfur compounds: few target molecules of general interest contain sulfur substituents and the thiopyran ring system is especially rare. Any advantage to be derived from a dihydrothiopyran for more general synthetic applications must therefore be compared to the effort required to prepare the sulfur heterocycle and to eventually remove the sulfur atom.

There are some example where the effort has been well worthwhile and where dihydrothiopyrans have offered obvious benefits in complex synthesis. The juvenile hormone routes of Kondo and Stotter (Scheme 1) employ the sulfur heterocycle to define trisubstituted olefin geometry and to build up a chain of repeating 6-carbon units [1]. Thus, anion 1 is alkylated to give 2 which can be dehydrated, deprotonated, and alkylated with an isoprenoid allylic chloride. After the proper skeleton is assembled, reductive sulfur removal (3 → 4) is performed and several steps lead to juvenile hormone.

Scheme 1



A conceptually related application of dihydrothiopyrans is found in the Woodward erythromycin synthesis (Scheme 2) [2]. Here, the bicyclic substrate 5 can be converted in several steps including osmylation with predictable stereocontrol to give an acetonide 6. This substance contains a carbon segment which resembles the environment and stereochemistry of erythronolide C_4—C_6 and C_{10} —C_{13} subunits. Thus, a series of simple steps including a classical Raney Ni (Ra-Ni) desulfurization converts 6 into the aldehyde 7. An alternative sequence from the same bicyclic sulfide 6 affords the enolate 8 which can be coupled with 7.

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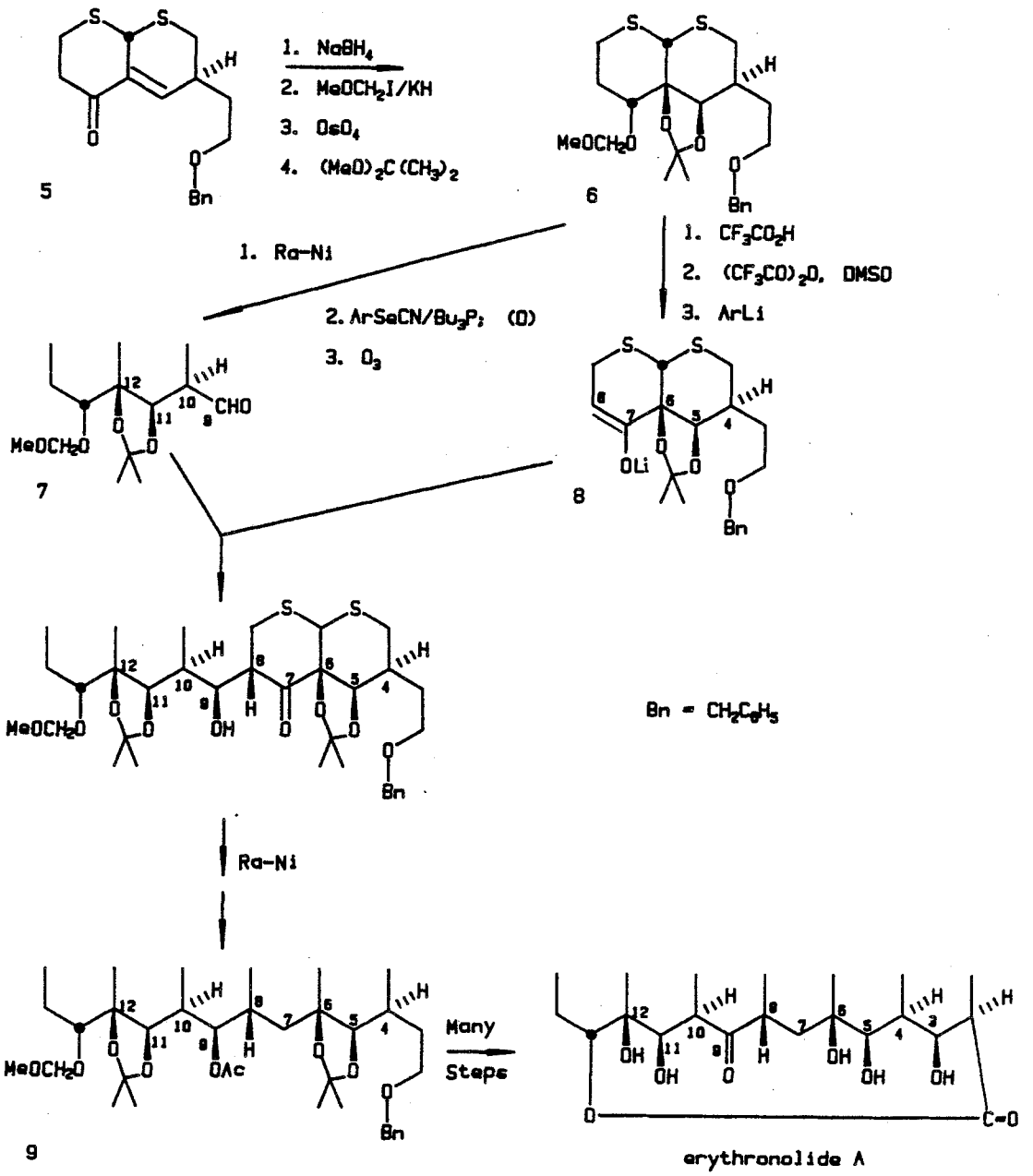
Scheme 2



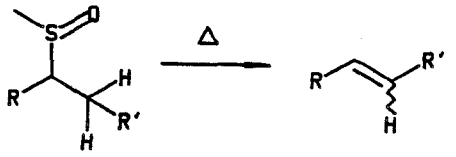
Eventually, sulfur is removed by the Ra-Ni method to give 9. The product 9 contains eight of the ten asymmetric centers of erythronolide and is an important intermediate in the total synthesis of erythromicin A.

Both of the complex examples (juvenile hormone, Scheme 1; erythronolide, Scheme 2) described so far use the dihydrothiopyran subunit in a passive but important role to control geometry. In the juvenile hormone synthesis, sulfur plays an additional active role in the coupling of subunits to build up the carbon skeleton. However, the most unique benefit from the dihydrothiopyran in both syntheses is that two different segments of the target structure are obtained from the same starting heterocycle. This strategic advantage justifies the effort needed to prepare cyclic sulfides or to remove sulfur reductively after it has served its purpose.

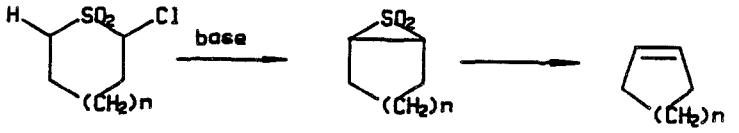
In the absence of such clear advantages, the reductive desulfurization strategy may not be the most efficient solution to typical synthetic problems. The intermediates contain sulfur functionality at carbons which are unsubstituted in the target structure and this can result in undesirable complexity. For that reason, further applications of dihydrothiopyrans

to synthesis will be discussed with emphasis on the utilization of C–S bonds as precursors of functional groups and not of CH bonds. This strategy can simplify the handling of intermediates because C–S bonds are relatively stable compared to some of the functional groups into which they can be converted. The most versatile methods for "nonreductive desulfurization" include:

1) the pyrolysis of sulfoxides to give alkenes by 5-center elimination [3]



2) the Ramberg–Bäcklund sulfur extrusion [4]

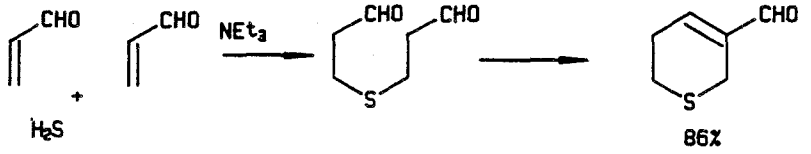


3) the oxidative conversion of C–S bonds into carbonyl derivatives. Examples of these methods will be described in the context of specific synthetic problems.

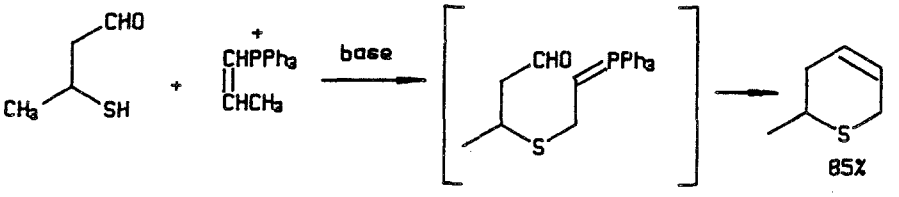
The potential utility of dihydrothiopyrans in synthesis also depends on the availability of general routes to the starting heterocycles. Scheme 3 lists a few of the recent examples of simple cyclization methods, including aldol [5, 6], internal Wittig [6], internal Friedel–Crafts acylation [7], and electrocyclic ring closure reactions [8]. Along these, only the aldol cyclization (Eq. 1) has seen much use. One interesting example is in the preparation of Woodward's erythronolide precursor 5 in optically active form [2]. The key cyclization (Eq. 2) occurs with asymmetric induction (36% *l*,*l*-form) upon use of D-proline as catalyst, and optically pure 5 can be obtained by crystallization.

Scheme 3

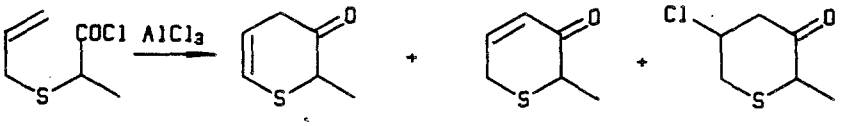
eq. 1 (ref. 5):



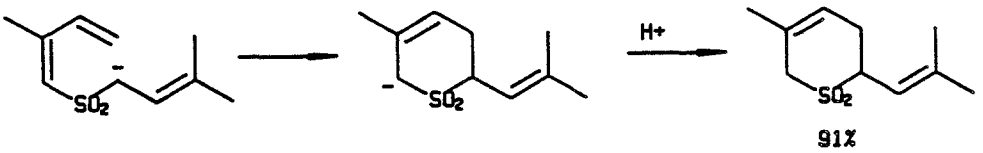
(ref. 6):



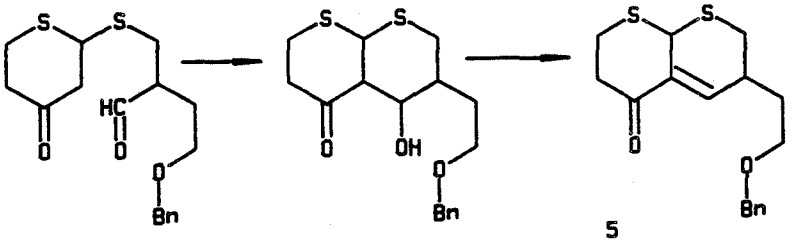
(ref. 7):



(ref. 8):



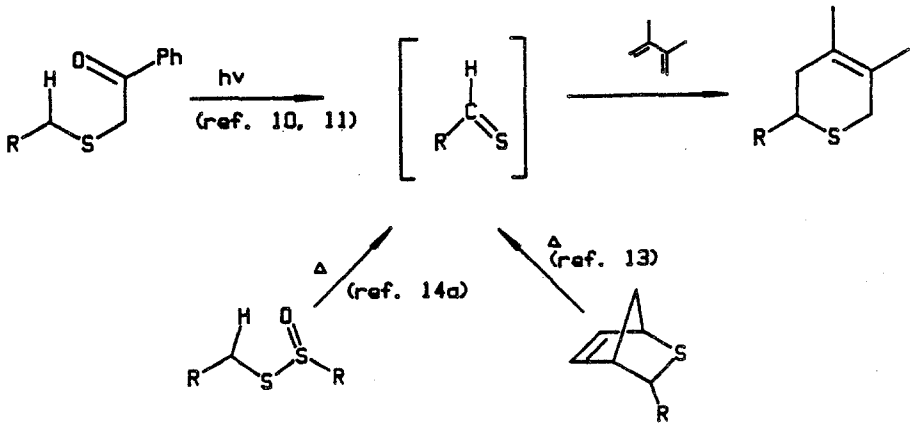
eq. 2 (ref. 2)



The most useful recent development in synthesis of dihydropyrans is the 2+4 cycloaddition reactions of thiocarbonyl dienophiles with 1,3-dienes. There are several examples of such reactions involving thioketones or activated dithioesters [9], but best results are obtained with thioaldehydes as the dienophiles [10-15]. Despite their bad reputation for polymerization, transient thioaldehydes react efficiently with electron-rich dienes and provide an excellent source of dihydrothiopyrans.

Several convenient methods for thioaldehyde generation have recently been developed. The photochemical method via sun lamp-induced cleavage of phenacyl sulfides is the most general and provides access to virtually all thioaldehydes (Scheme 4) [10, 11]. In cases where the diene is light-sensitive or relatively unreactive in the hetero-Diels–Alder reaction, thermal generation of thioaldehydes from their cyclopentadiene adducts can be a convenient alternative [13]. The starting cyclopentadiene adducts can usually be made by the photochemical method as well as by alternative techniques [14]. Thermal thioaldehyde generation from thiosulfinates also allows the convenient preparation of Diels–Alder adducts, [14a].

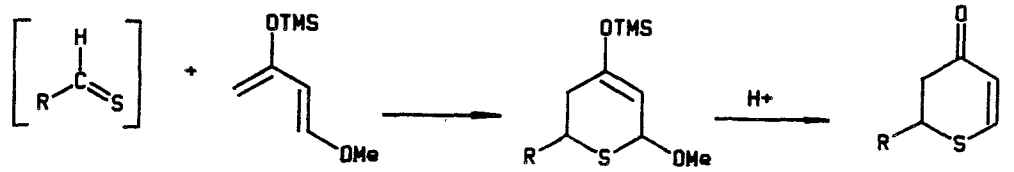
Scheme 4

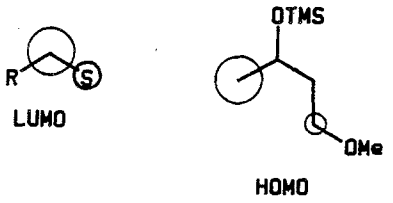


Dihydrothiopyrans are most easily obtained from electron-deficient thioaldehydes XCH=S (X = CN, acyl, ester, Ph_2PO, $PhSO_2$, etc.) (Table 1). The effect of an electron-withdrawing substituent is to lower thiocarbonyl LUMO energy and this results in improved dienophile LUMO–diene HOMO interactions [12]. Simple alkane or arene thials (RCH=S, ArCH=S) are more difficult to trap using the photochemical method, and it is helpful to use dienes with a high energy HOMO such as the Danishefsky diene. On the other hand, thermal thioaldehyde generation allows trapping with some of the less reactive dienes and this approach often gives the best yields of dihydrothiopyrans in the case of aromatic thial dienophiles [13, 14a].

Since the thioaldehyde always behaves as the LUMO component, the Danishefsky diene is an excellent trapping agent in all cases. However, the regiochemistry of trapping is strongly dependent on the thioaldehyde substituent, and alkanethials RCH=S afford adducts having the "meta" relationship between R and the diene alkoxy groups [11, 12]. The initial adducts obtained from the Danishefsky diene are unstable, and acid treatment converts them efficiently into dihydrothiopyrones:

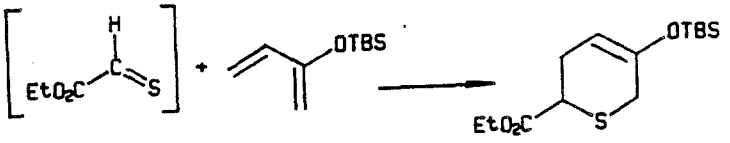
Scheme 5

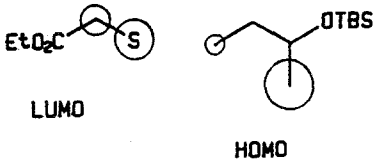




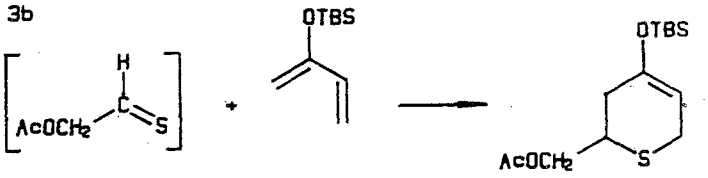
In FMO terms, the thiocarbonyl group in RCH=S has the larger LUMO coefficient at carbon and this interacts preferentially with the diene terminus having the larger HOMO coefficient [12]. The result is a trend for "meta" products which is also maintained with 1- or 2-monosubstituted butadienes (Table 2). Electron-deficient thioaldehydes XCH=S, however, behave in a strikingly different way. The effect of X on LUMO polarization is opposed to and stronger than the intrinsic polarization of the C=S bond. As a result, the regiochemistry of cycloadditions is reversed compared to the RCH=S reactions, and XCH=S affords ortho/para substituted dihydrothiopyrans with unsymmetrical dienes [12]. A typical example is given below involving the trapping of $EtO_2CCH{=}S$ (Eq. 3a). The opposite regiochemistry of cycloaddition can be achieved with synthetically equivalent substituents simply by using a thioaldehyde RCH=S having sp^3 hybridization at the α-carbon (Eq. 3b). Control for either regiochemistry is a powerful advantage and allows synthesis of virtually any dihydrothiopyran [11].

eq. 3a





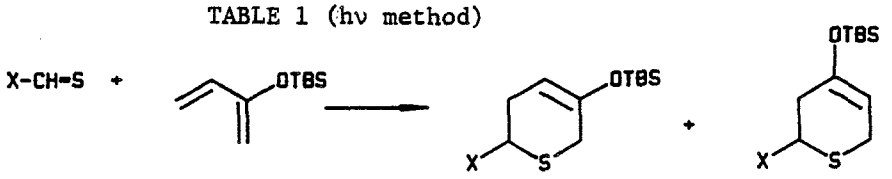
eq. 3b



The synthetic benefits to be gained from dihydrothiopyrans can be appreciated by considering the simple examples of 2+4 cycloaddition reactions of photochemically generated thio-

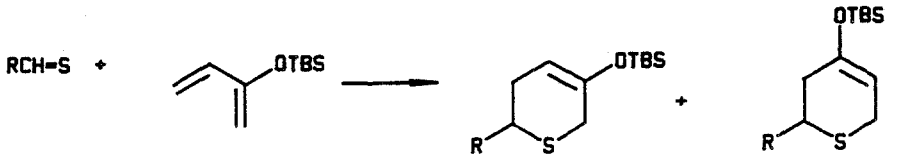
(ref. 11):

TABLE 1 (hν method)

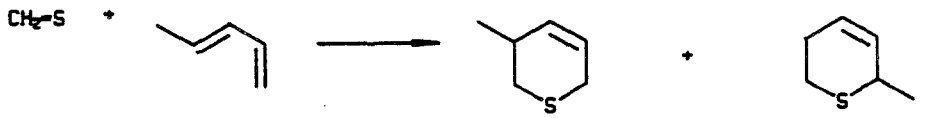


X = CH_3CO	43%	12%
PhCO	59%	5%
CN	70%	4%
$Ph_2P(O)$	75%	-
$PhSO_2$	57%	6%

TABLE 2 (hν method)



R = H	7%	67%
CH_2OAc	-	74%
Ph	5%	10%



21% 70%

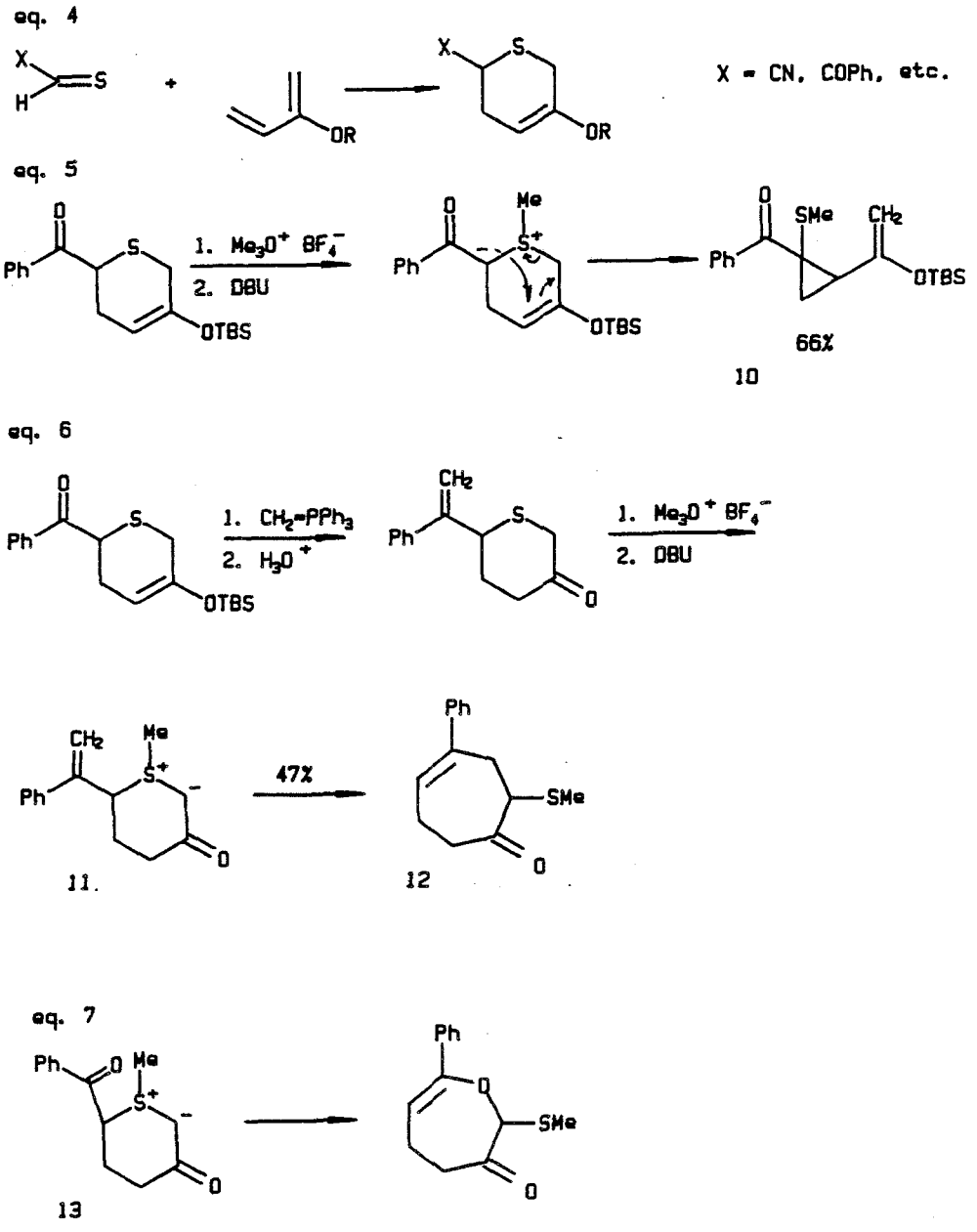
aldehydes given so far. A new carbon bond is created in the course of dihydrothiopyran formation and regiochemistry can be predicted. The reaction occurs under totally neutral conditions at 0° or below where numerous sensitive substitutents are stable. The potential for building carbon chains and unusual functionality in a complex substrate is clear, provided that these benefits of the sulfur reagents can be combined with convenient techniques for sulfur removal.

Thioaldehyde-derived dihydrothiopyrans have been used to greatest advantage in complex synthetic projects. However, some of the fundamental reactions can be appreciated by considering relatively simple examples. Scheme 6 illustrates some possibilities for construction of carbocyclic compounds from the 2+4 cycloadducts of 2-alkoxybutadienes and electron-deficient thioaldehydes. The regiochemistry of cycloaddition follows the expected pattern where acceptor (X) and donor (OR) groups are "para" (Eq. 4). Direct S-methylation of the cycloadduct followed by treatment with base (DBU) generates an ylide (Eq. 5). A facile 2,3-shift then occurs spontaneously and converts the ylide into a highly substituted cyclopropane 10 without disturbing the enol ether substituent [10].

A somewhat different 2,3-shift occurs when the same cycloadduct is converted into an ylide 11 as shown in Eq. 6. In this case, the 5-centered transition state leads to a 7-membered carbocycle 12. Interestingly, the closely related ylide 13, undergoes a similar rearrangement to give a 7-membered oxygen heterocycle (Eq. 7) [10].

A more complex carbocyclic example is described in Scheme 7 [16]. The cycloadduct obtained from a 2-siloxybutadiene and cyanothioformaldehyde (Eq. 4, X = CN) can be converted

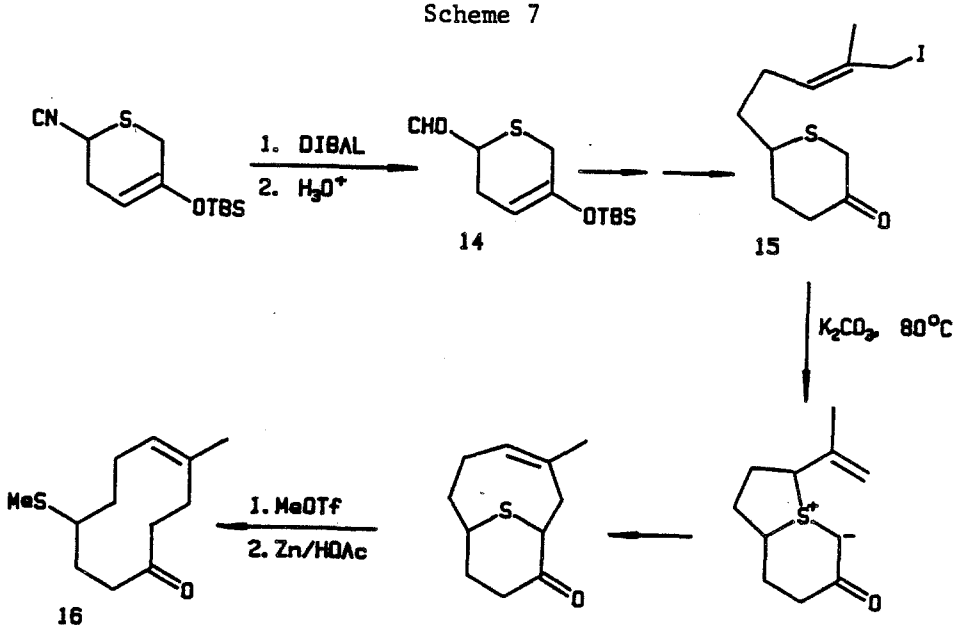
Scheme 6



into the aldehyde 14 by DIBAL reduction and imine hydrolysis. A series of Horner–Emmons condensations with appropriate functionality adjustments then leads to the allylic iodide 15. Upon heating in the presence of K_2CO_3, 15 affords an ylide via internal S-alkylation and deprotonation. An interesting variant of the 2,3-shift is now possible which creates a sulfur-bridged cyclodecenone, and S-methylation followed by reductive cleavage with zinc–acetic acid affords the carbocycle 16. In contrast to Ra-Ni desulfurization, this method preserves one C–S bond for possible conversion into other desirable functional groups as discussed later, and initially converts the other C–S bond into an enolate which can be used for a variety of synthetic transformations. A similar approach has been used to make 11-membered carbocycles [17], and an example in complex total synthesis will be discussed in the last section.

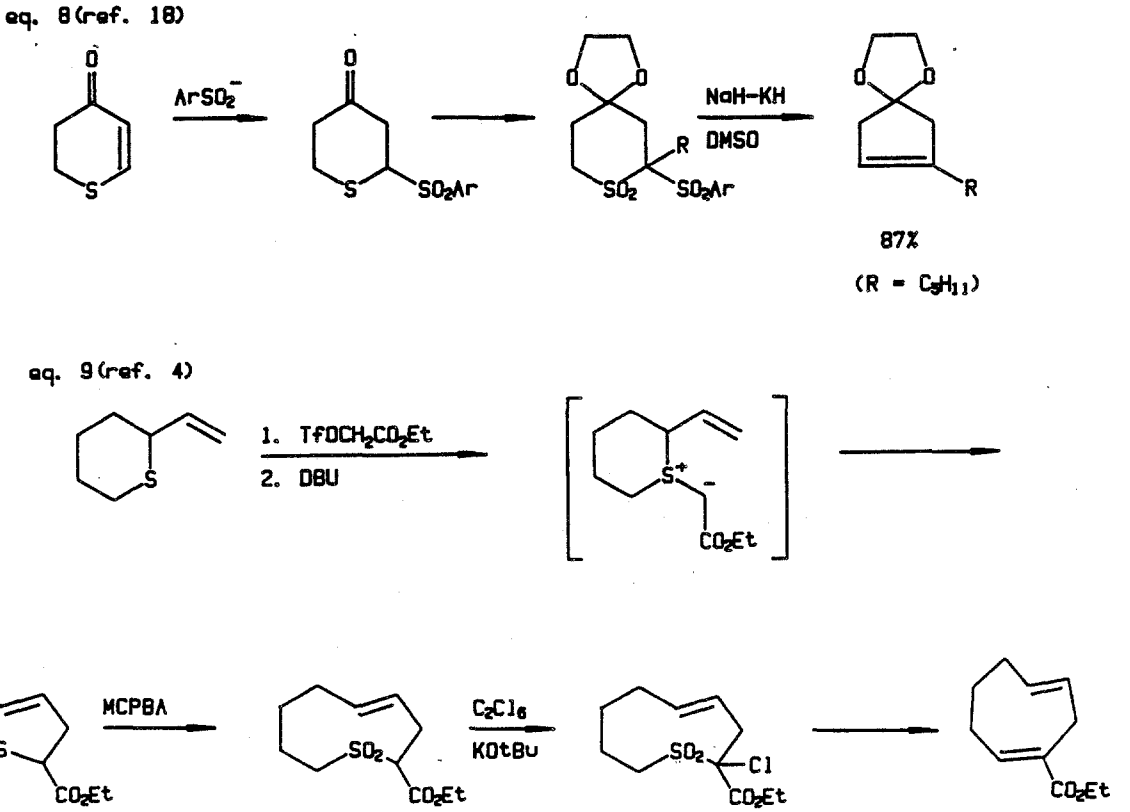
Other known routes to carbocycles can be related to thioaldehyde-derived dihydrothiopyrans in principle. Scheme 8 (Eqs. 8 [18], 9 [4]) illustrates examples of the classical Ramberg–Bäcklund method for alkene synthesis from cyclic sulfide precursors. The sulfone starting materials for Eq. 8 might be accessible by thioaldehyde cycloaddition based on the known sequence in Scheme 5. Although the level of difficulty in Scheme 5 is not high, the overall sequence could probably not compete with other known routes to cyclopentenes. On

Scheme 7



the other hand, Eq. 9 would easily compete with any known sequence for preparation of functionalized trans-cyclooctene derivatives, and the starting material is easily related to thioaldehyde cycloadditions. Sulfur-based approaches are best suited for relatively complex synthetic problems or for target molecules having unusual structural features which justify the effort needed to remove sulfur.

Scheme 8

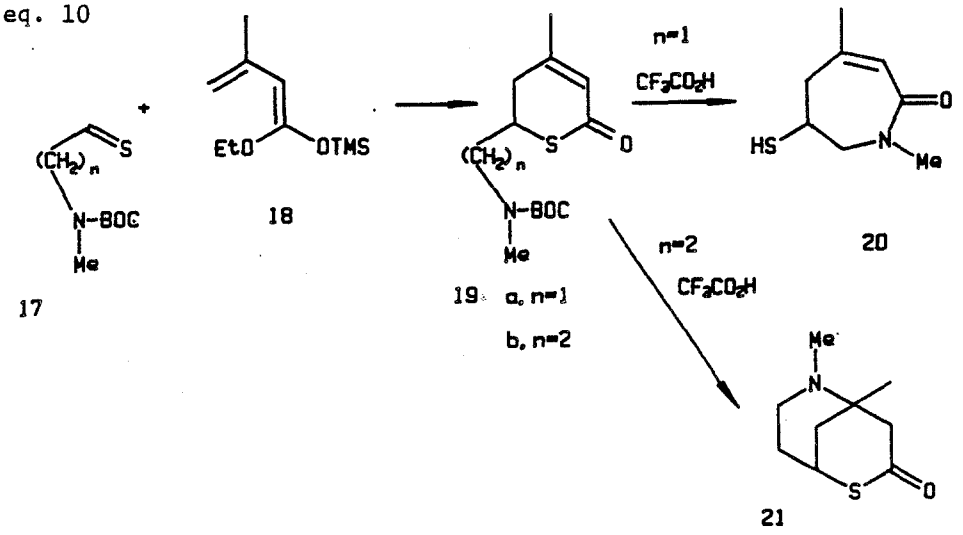


Access to medium- or large-ring heterocycles is possible from the adducts of alkane thials with oxygenated dienes. As shown in Eq. 10, the ketene acetal 18 affords unstable orthoester adducts with thioaldehydes 17 containing a protected nitrogen function [13]. Thiolactones 19 are formed during product isolation and, upon removal of the N-protecting group, 19a is converted spontaneously into the 7-membered lactam 20. However, the homologue 19b undergoes internal Michael addition instead of acyl transfer, and the product is a bycyclic amine 21. If the internal Michael addition is blocked, as in the saturated thiolactone 22, then acyl transfer again takes place and the lactam 23 is obtained (Eq. 11) [13].

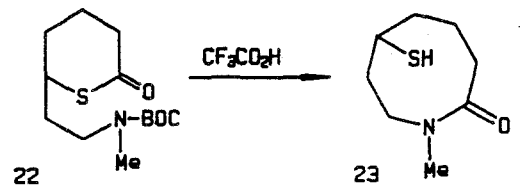
The acyl transfer process involved in the preparation of lactams 20 or 23 can also be used to make medium ring lactones [19]. With hydroxyalkyl-substituted thiolactones such as 24, acyl transfer from sulfur to oxygen does not go to completion because the increase in stability of an oxygen ester over the starting sulfur ester is not sufficient to overcome the strain energy of the 8-membered ring 25 [19a]. However, in larger rings there is little difference in strain energy and the acyl transfer step does go to completion. In a typical example, the 10-membered thiolactone 26 (prepared via dichloroketene-induced thio-Claisen rearrangement, Eq. 12) is converted into the 11-membered lactone 27 [19b]. Acid catalysis and gentle heating are required in typical S to O acyl transfer reactions, but the conditions are mild enough for use with complex molecules. In contrast to most direct cyclization methods for medium-sized ring synthesis, the acyl transfer approach to macrolides does not require high dilution techniques.

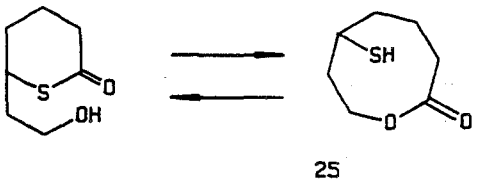
Scheme 9

eq. 10

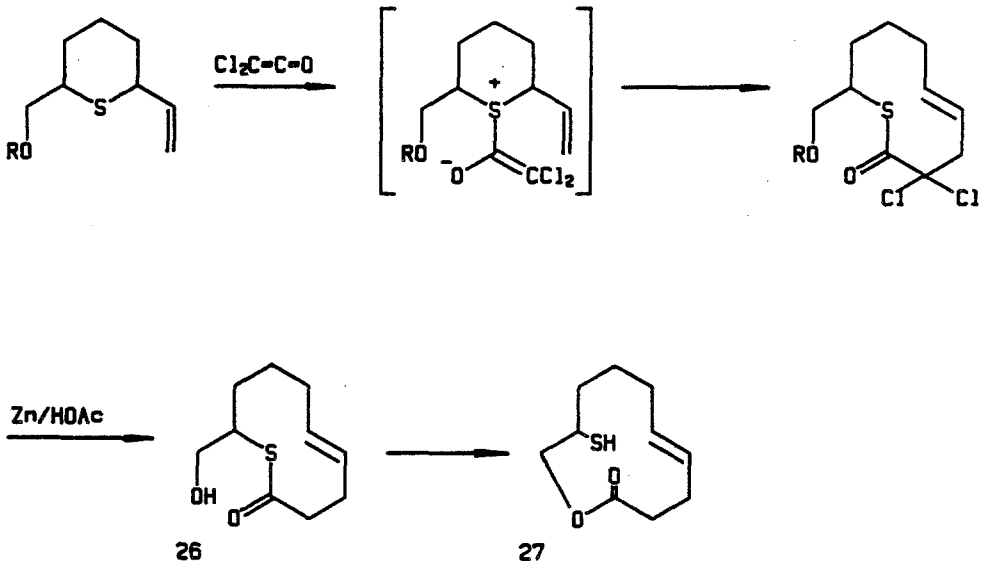


eq. 11





eq. 12

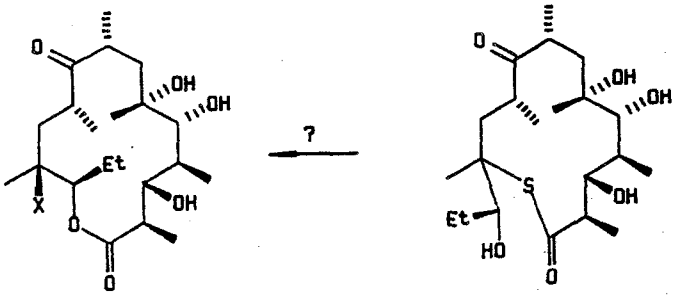


26 27

A combination of dihydrothiopyran and acyl transfer methodology is featured in our approach to macrolide antibiotics (Schemes 10, 11, 12). Complex 14-membered lactones such as the erythronolides 28 are derived in principle from thiolactones 29 by actyl transfer. A simple example of 14-membered lactone synthesis by a similar method has been demonstrated (Eq. 13) [19b]. This study also illustrates a mild technique for sulfur removal which can be used in the more complex macrolide environment. Conversion of the mercapto lactone 30 into phenacyl sulfide 31 followed by photochemical cleavage affords a thioketone 32. It is then possible to transform 32 into the sulfur-free ketone 33 via in situ trapping with a silyl nitronate ester (Eq. 14), followed by fluoride ion cleavage of the 2+3 cycloadduct [20].

The phenacyl sulfide cleavage is a general method for conversion of C–S bonds into the ketone or aldehyde oxidation level. However, our approach to macrolides also requires an oxidative method for conversion of a cyclic sulfide to a thiolactone. This problem can be solved by phosphenylation of sulfoxide anions with $ClPPh_2$. The initially formed sulfoxide phosphines (Eq. 15) undergo iodine-catalyzed oxygen migration from sulfur to phosphorus, and the resulting phosphine oxides can be converted by anion oxygenation into the desired thiol esters.

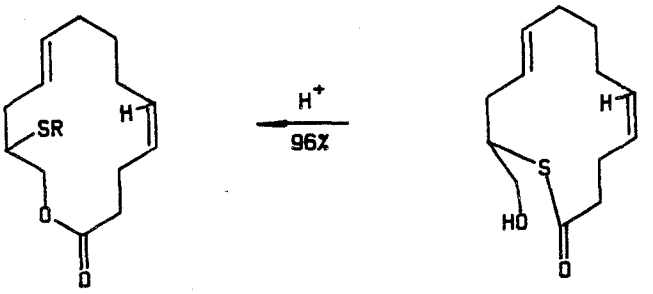
Scheme 10

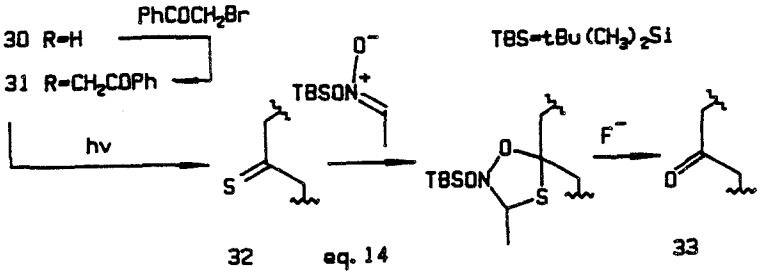


28 (erythronolides: X = OH) 29

(X=SH by acyl transfer)

eq. 13 (ref. 19b)





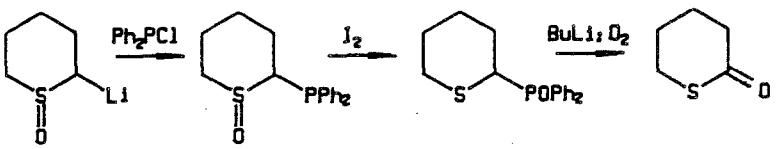
32 eq. 14 33

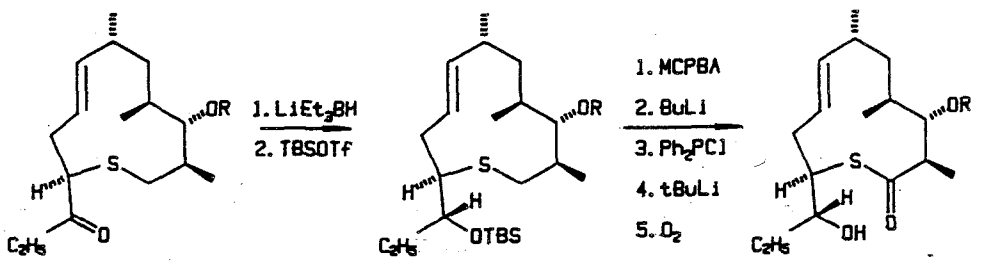
Scheme 11 demonstrates the use of these oxidative methods to convert an 11-membered sulfide into 12-membered macrolides of the methynolide family [22]. This synthesis features sulfur in a central role to build up the carbon skeleton by ylide ring expansion steps, but these steps do not involve dihydrothiopyrans and will not be described in detail. Sulfur also is important in control of methynolide C_{11} stereochemistry in the reduction of an α-acyl sulfide 34, Selective attack of the reducing agent on one face of the ketone 34 results from the large Felkin–Anh effect of sulfur in the transition state for hydride attack.

The first oxidative sequence is now used to convert 35 into the thiolactone 36 via sulfoxide and phosphine oxide intermediates. Acyl transfer occurs smoothly under acid catalysis to give the 12-membered lactone mercaptan 37 which affords the ketone 38 by the phenacyl sulfide photolysis method. Thus, each of the C–S bonds is converted into methynolide oxygen functionality. The first sequence involves strongly basic reagents and is restricted to relatively simple substrates, but the photochemical sulfur removal technique is mild and is ideally suited for complex molecules.

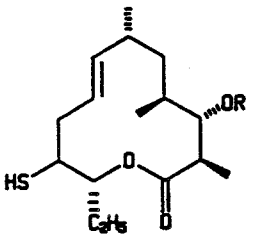
Scheme 11

eq. 15





34 35 36



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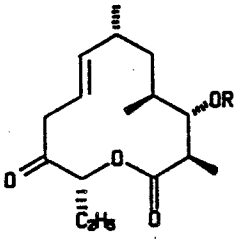
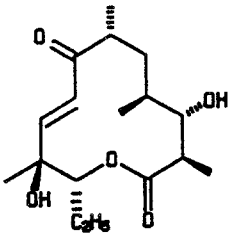


38



methynolide

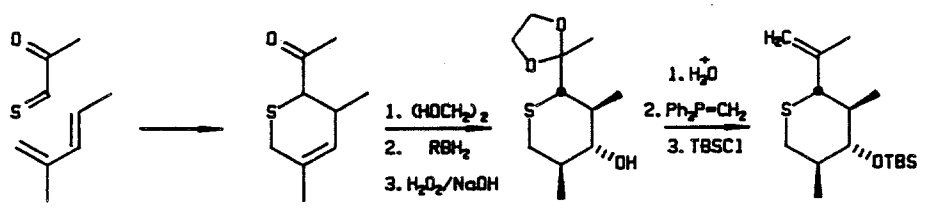
The same overall strategy is planned in our approach to erythronolides (Scheme 12) [23]. A dihydrothiopyran 39 is made by 2+4 cycloaddition of transient thiopyruvaldehyde, generated by the photochemical method. Regiochemistry follows the ortho, para substituent preference seen with electron-deficient thioaldehydes and there is modest selectivity for the stereoisomer expected from the "endo" transition state involving maximal secondary orbital interaction. Protection of 39 as the ketal results in equilibration to the all-equatorial isomer, and olefin hydroboration occurs from the less hindered side to give 40. This substance contains the C_2–C_4 relative stereochemistry of erythronolides.

After protecting group mainpulations and Wittig olefination, 41 can be converted ito the 9-membered ring 43 via the 2,3-sigmatropic shift of an ylide 42. This sequence involves a typical sulfur ylide ring expansion and the product is formed with a strong preference for the E-olefin geometry. Due to local conformational preferences near the double bond, selective osmylation and protection can now be performed on the indicated conformer to give acetonide 44 which has 5 of the asymmetric centers of erythronolide correctly placed.

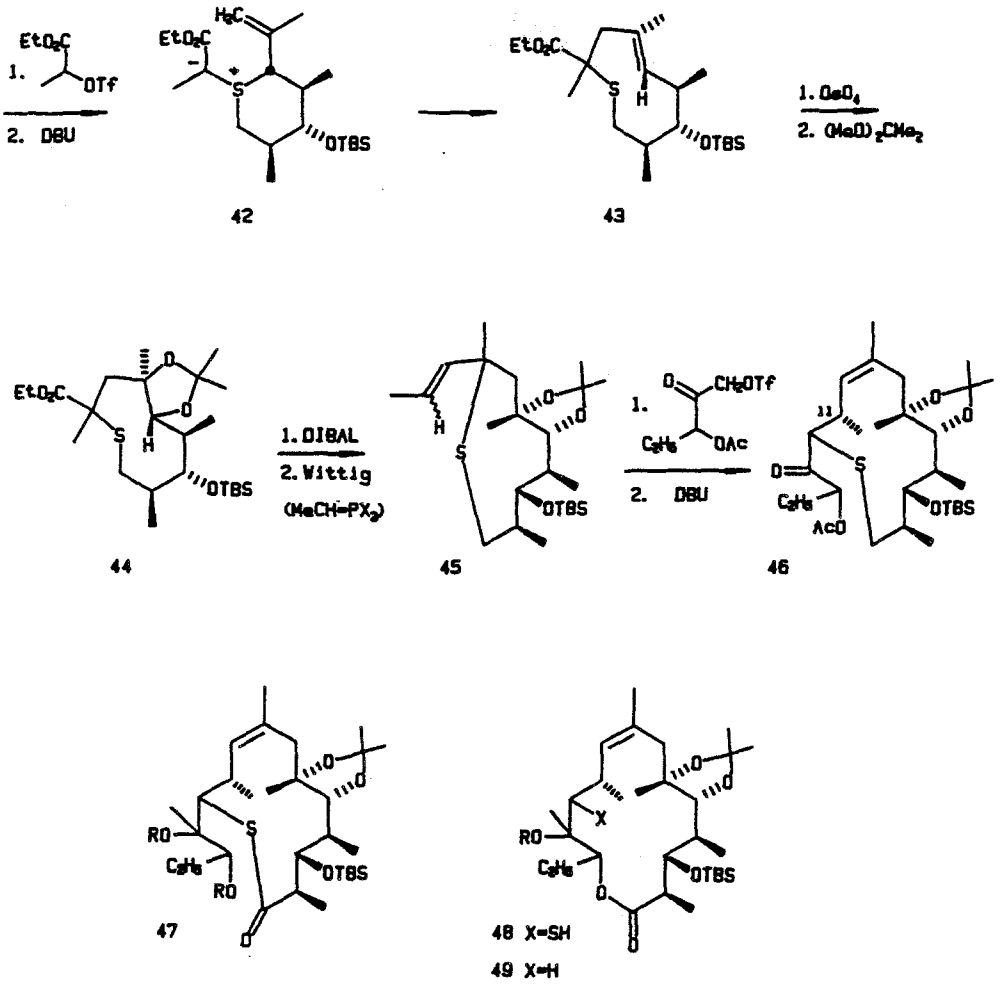
After a sequence of classical steps, 45 can be subjected to a second ring expansion to give a 12-membered sulfide 46. Either the natural or the unnatural C_{10}-methyl diastereomer can be made exclusively, depending on the propenyl sidechain geometry in 45, Both isomers of 45 are available by selective Wittig olefination of the precursor aldehyde. The Z-propenyl isomer is made using the standard Wittig reagent $Ph_3P{=}CHCH_3$, while the E-isomer is obtained exclusively with the unusual aminophosphorane reagent $(Et_2N)_3P{=}CHCH_3$ [24].

Sulfide 46 contains all of the carbons of erythronolide, and must now be carried through the oxidative acyl transfer and sulfur removal steps. These transformations have not yet been attempted, but the key intermediates would be the thiolactone 47, the acyl transfer product 48, and the reductive sulfur removal product 49. The plan for these steps resembles the methynolide sequence except that final sulfur removal uses the reductive desulfurization procedure. Desulfurization is planned by Bu_3SnH reduction of the mercaptan [19a] to avoid overreduction which is often associated with the Ra-Ni method. Although this strategy "wastes" one of the C–S bonds by conversion into C–H, alternative strategies do not allow as convenient a ring expansion sequence.

Scheme 12



39 40 41

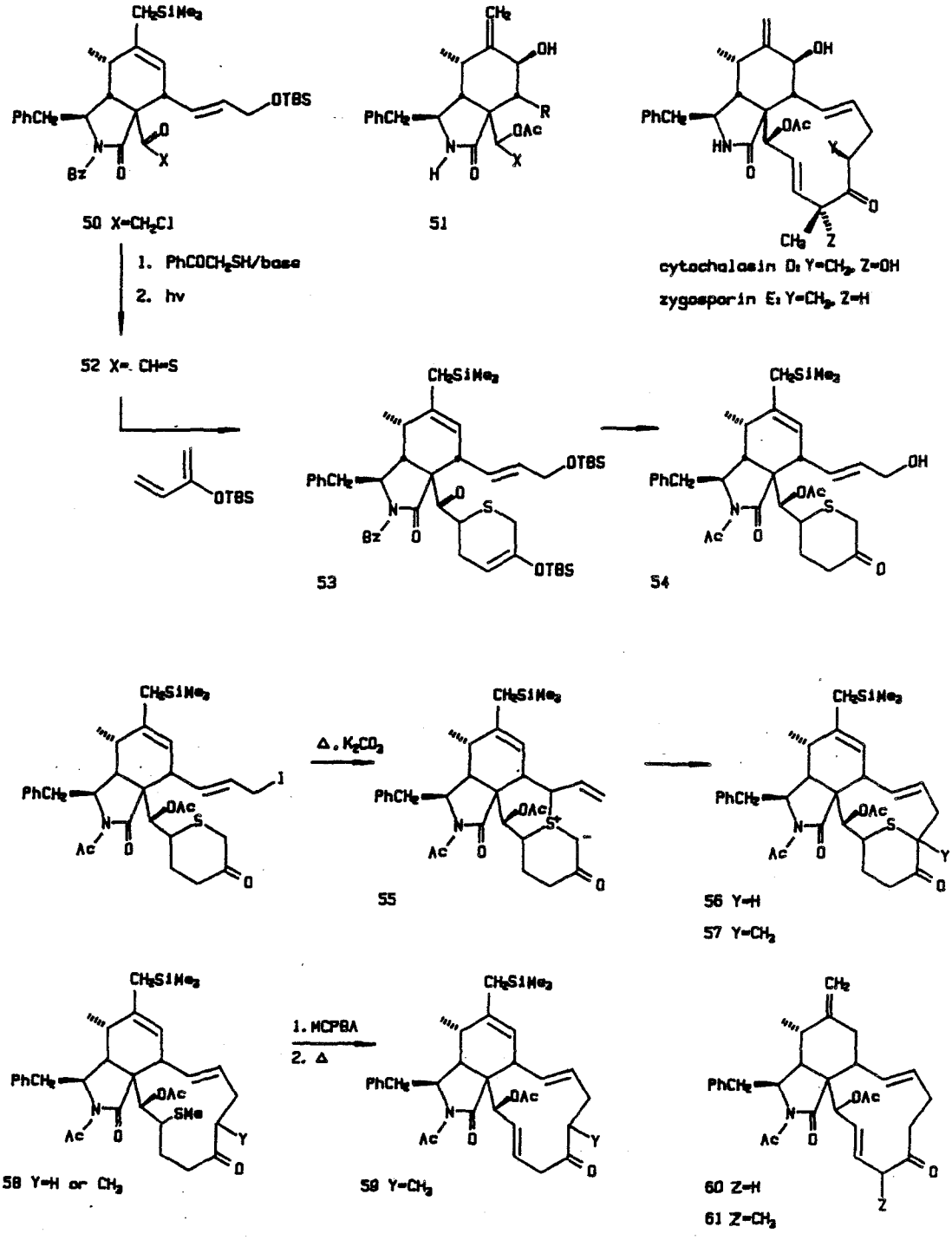


The last complex application of dihydrothiopyrans (Scheme 13) is taken from our synthesis of cytochalasin carbocycles [25]. It was this project which first encountered a need to connect C—C and C—S bonds using the thioaldehyde/dihydrothiopyran methodology. The bicyclic subunit 50 was prepared by a classical Diels—Alder route, and methods for conversion to the functionality pattern 51 common to most of the biologically active cytochalasins were well worked out [26]. However, introduction of the 11-membered carbocycle by sulfur-mediated methods proved difficult because classical methods for attachment of a sulfur ring as in 54 proved cumbersome in this complex environment.

The problem is efficiently solved by thioaldehyde methodology [25]. Phenacyl sulfide photolysis generates the thial 52 as usual, and Diels—Alder trapping affords the dihydrothiopyran 53 in good yield. Reduction of the keto function is done with Bu_2AlH to achieve natural product stereochemistry, and silyl ether cleavage affords the crucial intermediate 54. The reduction stereochemistry is dictated by sulfur stereochemistry which results from unknown kinetic effects at the stage of thioaldehyde trapping, and is favored even more by base-induced equilibration. Use of nonchelating reducing agents converts 53 into the hydroxyl diastereomer of 54 due to the Felkin—Anh effect.

Carbocycle formation from 54 now follows the same path as in the simpler example of Scheme 7. An ylide 55 is generated by internal sulfur alkylation and base-induced deprotonation, and 2,3-sigmatropic shift forms the sulfur bridged carbocycle 56. Surprisingly, this substance is methylated at the bridgehead position by treatment with LDA and methyl iodide to give 57, and C—S cleavage by zinc reduction of the corresponding sulfonium salt affords the cytochalasin ring system as in 58. Despite the complexity of 58, thermal sulfoxide elimination occurs smoothly to form the sulfur-free structure 59. A variety of derivatives can be made using similar methods, including 60 and 61 which are obtained by protodesilylation and which closely resemble naturally occurring cytochalasins and zygosporins [25, 27].

Scheme 13



In conclusion, it is correct to say that dihydrothiopyrans can play a useful role in organic synthesis. We have emphasized the applications to preparation of complex medium-sized rings, problems which stimulated the development of thioaldehyde cycloaddition methodology and the technology for oxidative removal of sulfur substituents. The role of sulfur heterocycles in the synthesis of simpler structures depends on further improvements in these techniques. However, the availability of dihydrothiopyran starting materials is no longer a problem, and practical access to these heterocycles should encourage continuing progress on the efficient conversion of sulfur into other useful functionality.

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