# CENTENARY LECTURE*

# Cyclopentanoids: A Challenge for New Methodology

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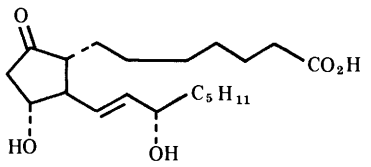
## 1 Introduction

The chemistry of six-membered rings plays a dominant role in synthetic organic chemistry, in part, because of the widespread occurrence of such a structural feature in many biologically important natural products. Prior to the early sixties, except for a few classical examples such as the iridoids and cedranes and as a singular appendage to six-membered rings as for the steroids, cyclopentanoids and especially polycondensed cyclopentanoid natural products were rare.[1] Development of synthetic strategy to such systems was overshadowed by the pre-occupation with their six-membered ring counterparts. The identity of prostaglandins as cyclopentane derivatives [*e.g.* $PGE_2$, (1)[2]] and the elucidation of the structure of hirsutic acid[3] (2) as a terpene possessing three fused five-membered rings initiated a continuing revelation of many varied cyclopentane natural products, some of which are listed in Figure 1.

Synthetic solutions to such a marvellous array of structural types will undoubtedly benefit from a plethora of five-membered ring forming reactions. Classical reactions such as Dieckmann cyclizations, Friedel–Crafts acylations, and aldol condensations clearly apply to these systems as well as other ring sizes. However, in these and other reactions, *e.g.* intramolecular alkylations, special problems accrue to the formation of the somewhat strained five-membered ring. For example, whereas application of the aldol condensation for the synthesis of (3; equation 1), a well-known building block in natural products synthesis known as the Wieland–Miescher ketone, succeeds admirably, the corresponding reaction for formation of (4; equation 2) requires quite special conditions and then only proceeds in 30—40% yield.[4] Intramolecular alkylations such as that represented in equation 3 suffer from a stereoelectronic bias for *O*-

*The present text is based upon the lecture delivered on the 11 March 1982 at a RSC Perkin Division Meeting at the Scientific Societies' Lecture Theatre, Savile Row, London W1.

[1] T. K. Devon and A. I. Scott, 'Handbook of Naturally Occurring Compounds,' Vol. I and II, Academic Press, New York, 1972.
[2] A. Mitra, 'The Synthesis of Prostaglandins,' John Wiley & Sons, New York, 1977.
[3] F. W. Comer, F. McCapra, I. H. Qureshi, and A. I. Scott, *Tetrahedron*, 1967, **23**, 4761; F. W. Comer and J. Trotter, *J. Chem. Soc. B*, 1969, 11.
[4] W. G. Dauben and D. J. Hart, *J. Org. Chem.*, 1977, **42**, 3787.



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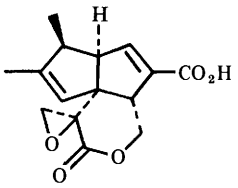
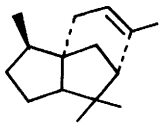
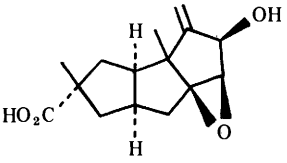


Pentalenolactone



Cedrene



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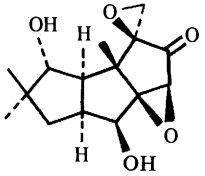
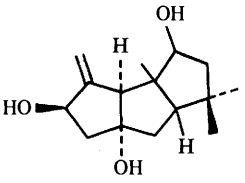
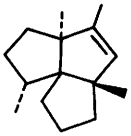


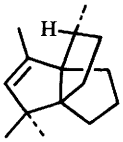
Coriolin



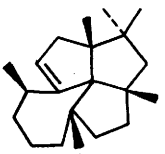
Capnellane



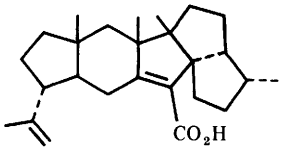
Isocomene



Modhephene

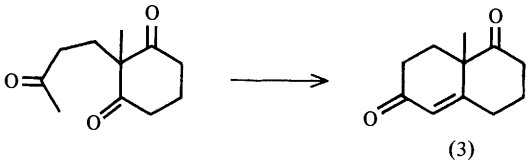


Laurene



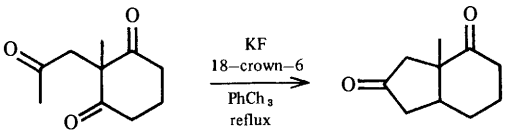
Retigeranic acid

**Figure 1** *Representative cyclopentanoid natural products*

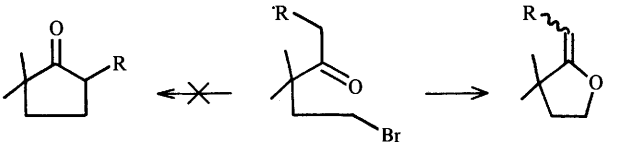


(3)

(1)




(4) (2)

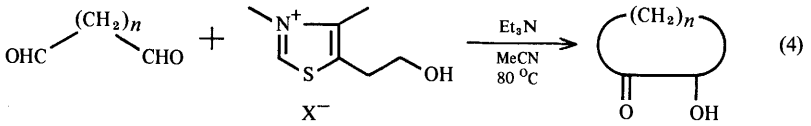


(3)

rather than *C*-alkylation, again in contrast to the six-membered ring case, which leads smoothly *via* normal *C*-alkylation.[5]

## 2 Cyclization *via* Acyl Anions

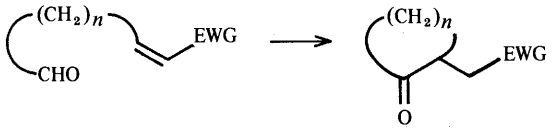
Many methods that apply to six-membered rings do translate over to five-membered rings. One of the most general cyclization methods known is the acyloin condensation, which appears to apply to virtually any ring size.[6] A related reaction is the redox coupling of an $\alpha,\omega$-dialdehyde with a thiazolium salt (equation 4).[7] Such a reaction would appear to proceed through the




(4)

equivalent of an acyl anion formed *in situ* between the thiazolium salt and the aldehyde.[8]

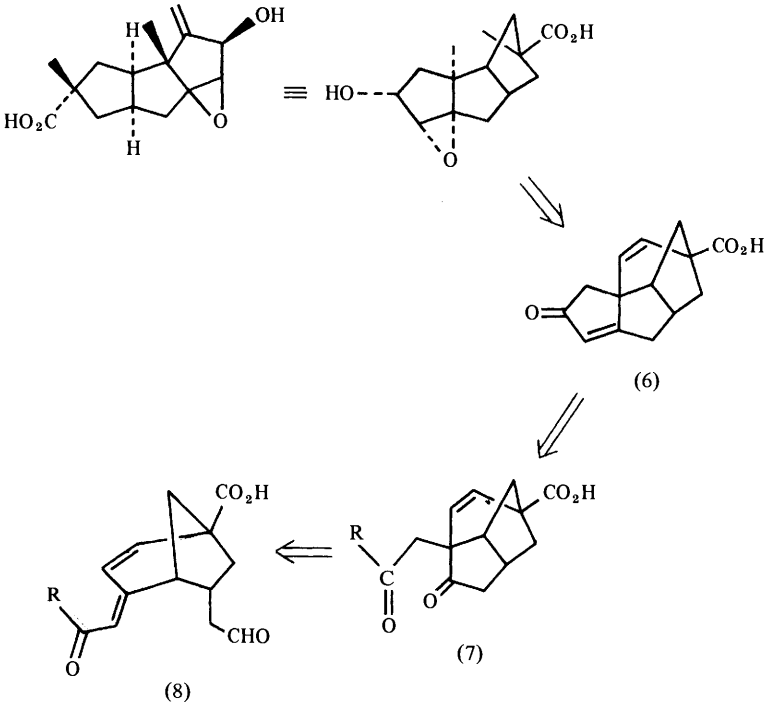
The ability to add such acyl anion equivalents in conjugate fashion to $\alpha,\beta$-unsaturated carbonyl systems suggests the possibility of an intramolecular version of the type illustrated in equation 5. Such an approach would lend itself



(5)

[5] J. E. Baldwin and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 1977, 233; H. O. House, W. V. Phillips, T. S. B. Sayer, and C. C. Yau, *J. Org. Chem.*, 1978, **43**, 700.
[6] J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, 1976, **23**, 259.
[7] R. C. Cookson and R. M. Lane, *J. Chem. Soc., Chem. Commun.*, 1976, 804.
[8] H. Stetter and H. Kuhlmann, *Chem. Ber.*, 1976, **109**, 2890: H. Stetter, W. Basse, and K. Wiemann, *ibid.*, 1978, **111**, 431.

to an attractive solution of polycondensed cyclopentanoid natural products such as hirsutic acid (5).[9] As Scheme 1 illustrates, a tetracycle such as (6)

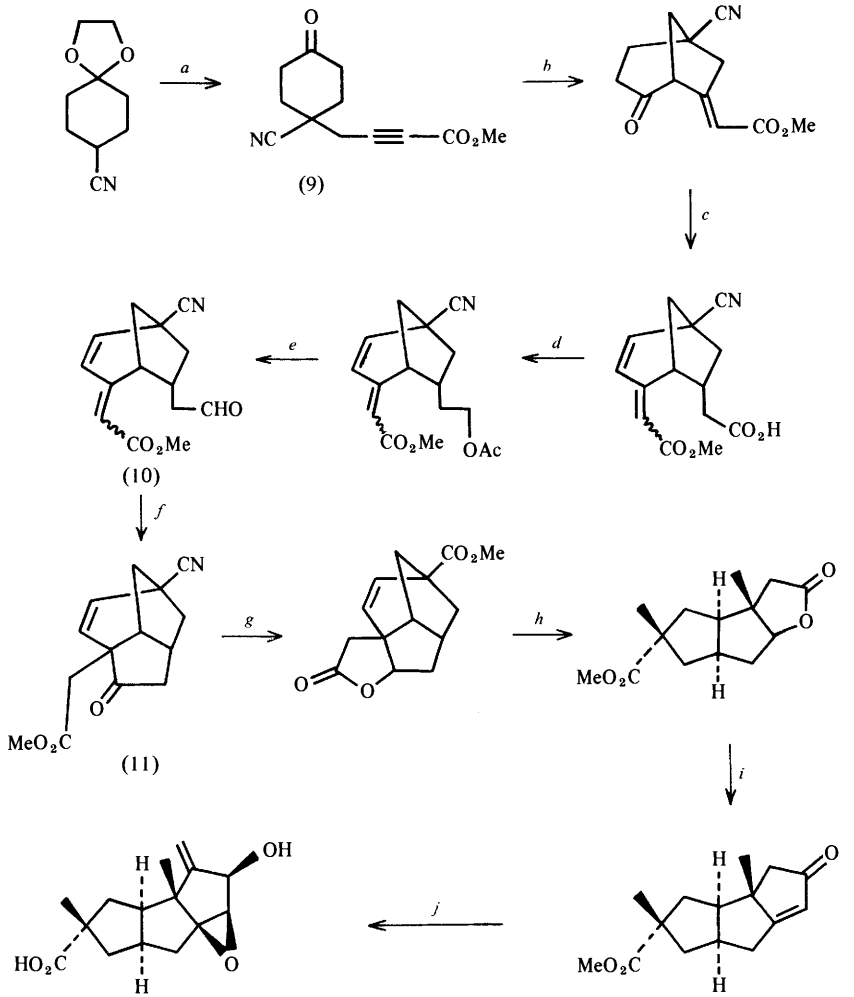



**Scheme 1** *Retrosynthetic analysis of hirsutic acid*

possesses the basic carbon skeleton of this terpene. The tricycle (7) represents a logical precursor that, by application of the principle represented in equation 5, simplifies to a bicyclo[3.2.1]octane (8). Simplification to a bridged bicyclic skeleton allows the stereochemical bias of such a system to resolve the problem of controlling the stereochemistry of hirsutic acid.

Scheme 2 summarizes this synthetic approach. Gratifyingly, the crucial cyclization of (10) to (11) proceeded routinely in 65—70% yields using triethylamine in hot isopropanol. The conjugate addition to the ynoate in (9) to produce the first five-membered ring offers an opportunity to explore an asymmetric synthesis. Indeed, use of quinine in this step gave a 65:35 mixture of enantiomers. Thus, intramolecular conjugate additions create five-membered rings with an efficiency comparable to other ring sizes.

[9] B. M. Trost, C. D. Shuey, and F. DiNinno, Jr., *J. Am. Chem. Soc.*, 1979, **101**, 1284.

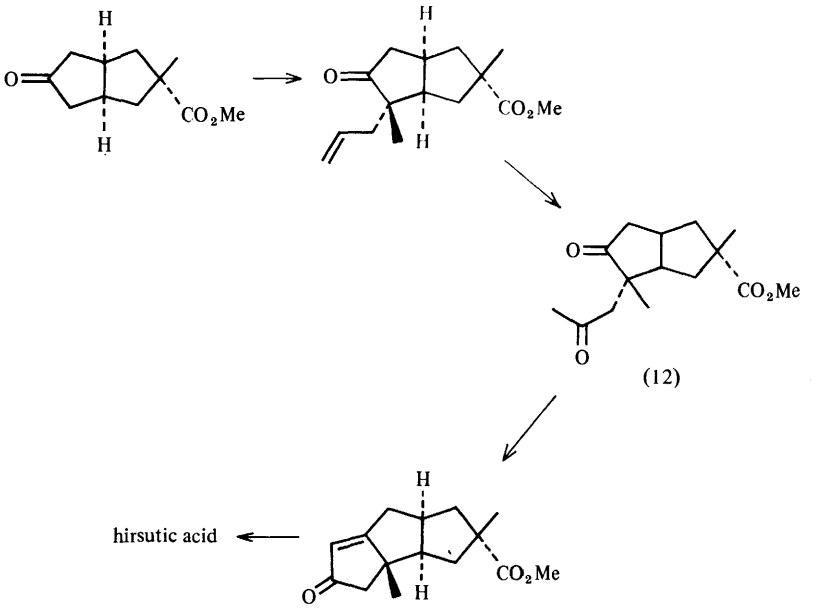



Reagents: (*a*): i, LDA, TMS—≡—$CH_2I$, THF; ii, KOH, MeOH; iii, LDA, THF, TMEDA, $CO_2$; iv, $CH_2N_2$, ether; v, $H_2SO_4$, $H_2O$, 78%. (*b*); $Et_3N$, $PhCH_3$, 75%. (*c*): i, $H_2$, $Pd/BaCO_3$, EtOH–EtOAc; ii, $BrZnCH_2CO_2C_2H_5$, PhH, ether; iii, NaOMe, MeOH, 77%. (*d*): i, $BH_3$.THF; ii, $Ac_2O$, $C_5H_5N$, 67%. (*e*): i, NBS, $CCl_4$; ii, LiBr, $Li_2CO_3$, DMF; iii, PCC, $CH_2Cl_2$, NaOAc, 64%. (*f*); 3,4-dimethyl-5-β-hydroxyethylthiazolium iodide, $Pr^iOH$, 67%. (*g*): i, $K_2CO_3$, MeOH; ii, $NaBH_4$, MeOH, THF; iii, $Ph_3P$, $MeO_2CN{=}NCO_2Me$, 92%. (*h*): i, HCl, MeOH, ether; ii, $O_3$, MeOH then $Me_2S$; iii, MeSH, $BF_3$.ether; iv, W-5 Raney Ni, EtOH, 75%. (*i*): i, KOH, THF, $H_2O$; ii, MeMgBr, ether; iii, PCC, $CH_2Cl_2$, NaOAc; iv, $KOBu^t$, THF, 46%. (*j*); performed by the procedure of Matsumoto *et al.* ref. 63

**Scheme 2** *A synthesis of hirsutic acid*

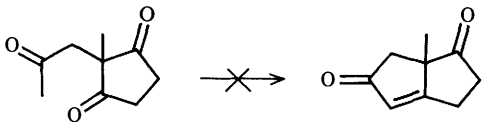
### 3 Cyclization *via* Olefination Reactions

A cyclopentenone annulation *via* a 1,4-diketone such as (12) requires a 2-oxopropylene equivalent. The general applicability of the Wacker oxidation[10]




(12)

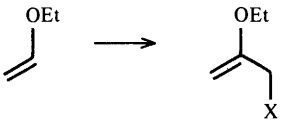
allows a simple allyl group to serve this purpose.[11] However, this method relies on the applicability of the direct aldol condensation for the final cyclization. The synthesis of a potentially useful building block, the bis-nor-Wieland–Miescher ketone (13), cannot be approached by this method.




(13)

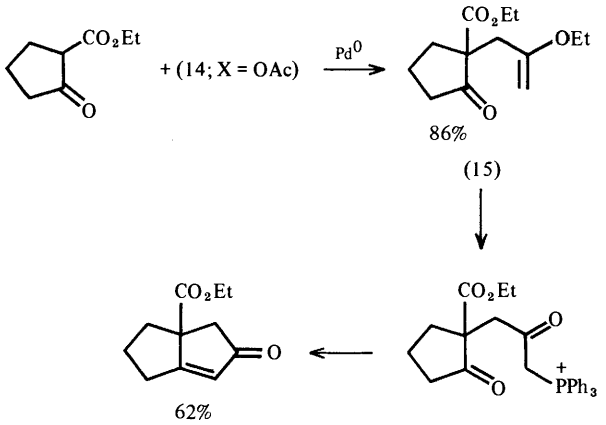
Circumvention of this problem invokes the use of an olefination procedure, which required development of a three-carbon synthon that permitted chemoselective conversion into the desired ylide. An enol ether such as (14) would be ideal since it would permit the chemoselective conversion of the side chain carbonyl group to the desired functionality. Although (14; X = Br) has been

[10] J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, 1976, 2975.
[11] M. Yamazaki, M. Shibasaki, and S. Ikegami, *Chem. Lett.*, 1981, 1245.



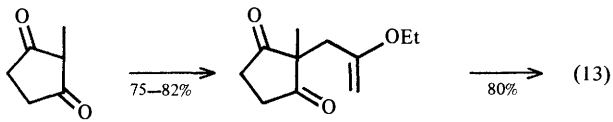
(14)

used as a 2-oxopropylene equivalent,[12] the difficulties associated with its synthesis, its lability, and the fear that *O*-alkylation of 1,3-dicarbonyl substrates would dominate led to the synthesis of (14; X = OAc) from ethyl vinyl ether and formaldehyde.[13] Palladium(0)-catalysed alkylation of 2-carboethoxycyclopentanone led to the smooth generation of the alkylated product (15). Sequen-



tial treatment of the enol ether with NBS in moist DMSO, triphenylphosphine in hot benzene, and aqueous potassium carbonate produces the stabilized phosphorus ylide, which smoothly cyclizes in refluxing methylene chloride.[13,14]

Application of this identical series of reactions to 2-methylcyclopentan-1,3-dione led *via* (16) to bis-nor-Wieland–Miescher ketone (13; m.p. 41—43 °C).



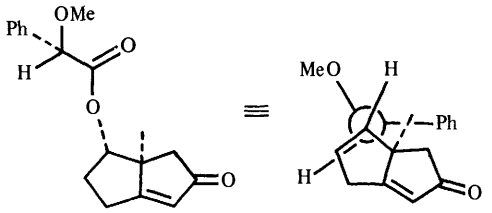
(16)

[12] R. M. Jacobson, R. A. Raths, and J. H. McDonald III, *J. Org. Chem.*, 1977, **42**, 2545.
[13] B. M. Trost and D. P. Curran, *J. Am. Chem. Soc.*, 1980, **102**, 5699.
[14] R. O. Clark, L. G. Kozar, and C. H. Heathcock, *Synth. Commun.*, 1975, **5**, 1; E. Piers, B. Abeysekera, and J. R. Scheffer, *Tetrahedron Lett.*, 1979, 3279; H. H. Aldenback, *Angew. Chem., Int. Ed. Eng.*, 1979, **18**, 940.

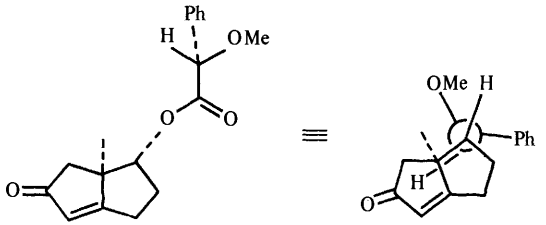
The use of chiral phosphines produced (13) with enantiomeric excesses of up to 77%.[15] By employing the *O*-methylmandelate ester (17), n.m.r. spectroscopy permitted assignment of the absolute configuration. Using the Mosher model[16] depicted in an 'extended Newman' projection in which the circle represents



—O—C— in an anti-array, the absolute stereochemistry depicted in (17a) can be assigned to the compound having more upfield shifts for the methyl group and the methylene group to the carbonyl group, compared to (17b). This little



(17a)



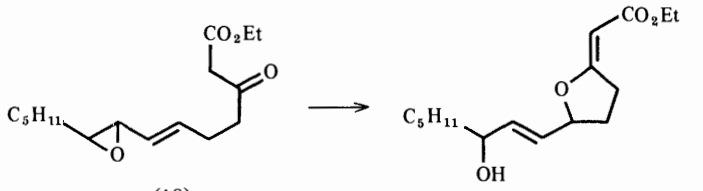
(17b)

used method has proved generally valid in assigning and analysing the degree of absolute stereochemistry, which when combined with the ease of resolution of *O*-methylmandelate esters on h.p.l.c., make such derivatives the ones of choice to resolve alcohols.

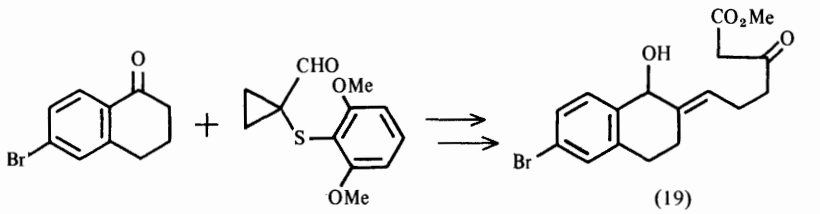
## 4 Cyclization *via* Alkylation Methods

Attempts to cyclize β-ketoesters such as (18) not unexpectedly generated the products of *O*- rather than *C*-alkylation.[17] This same observation plagued the cyclization of (19), a type of substrate that can readily be derived by straight-

[15] B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, 1981, **22**, 4929.
[16] J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.
[17] J. Martel, A. Blade-Font. C. Marie. M. Vivat. E. Toromanoff, and J. Buendia, *Bull. Soc. Chim. Fr.*, 1978. II, 131.



(18)



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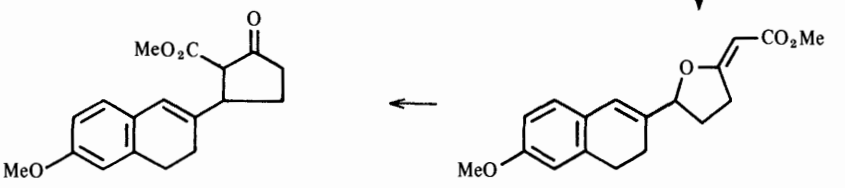
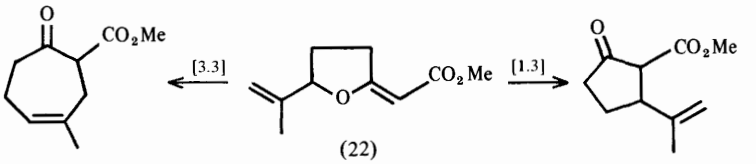


(21) (20)

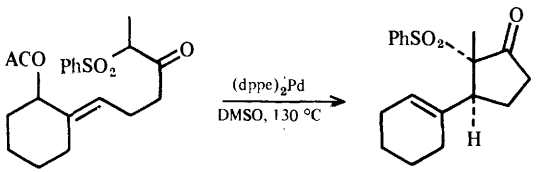
forward manipulation of the aldol condensation product of a ketone (*e.g.* 6-bromotetralone) and 1-arylthiocyclopropane-1-carboxaldehyde.[18] Although an imine derivative of (18) resolved this problem in this case, a more direct approach envisages a [1.3] rearrangement of the *O*-alkylated product to the thermodynamically more stable *C*-alkylated one. Thermal reorganization of 2-alkylidene-5-vinyltetrahydrofurans such as (22) leads *via* a [3.3] pathway to produce cycloheptenones.[19] On the other hand, palladium(0) catalysts permute the reaction profile of these allylvinyl ethers so that they now follow a [1.3] rearrangement pathway to 3-vinylcyclopentanones. Indeed, exposure of (20) to



(22)

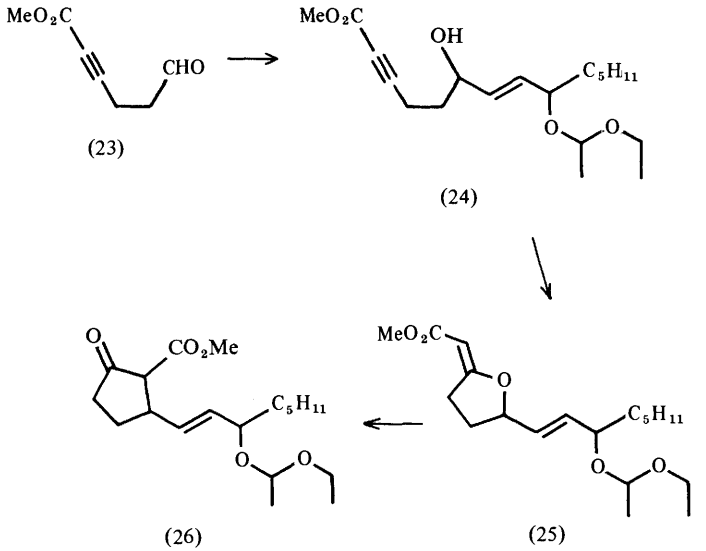
[18] B. M. Trost and L. N. Jungheim, *J. Am. Chem. Soc.*, 1980, **102**, 7910.
[19] B. M. Trost and T. A. Runge, *J. Am. Chem. Soc.*, 1981, **103**, 7550.

such a catalyst isomerizes it to the cyclopentanone (21), a steroid precursor. Since palladium(0) catalysts can initiate the *O*-alkylation and then subsequently rearrange that product, a one-pot cyclization of an acyclic precursor to a cyclopentanone can be accomplished as shown in equation 6.




52% (6)

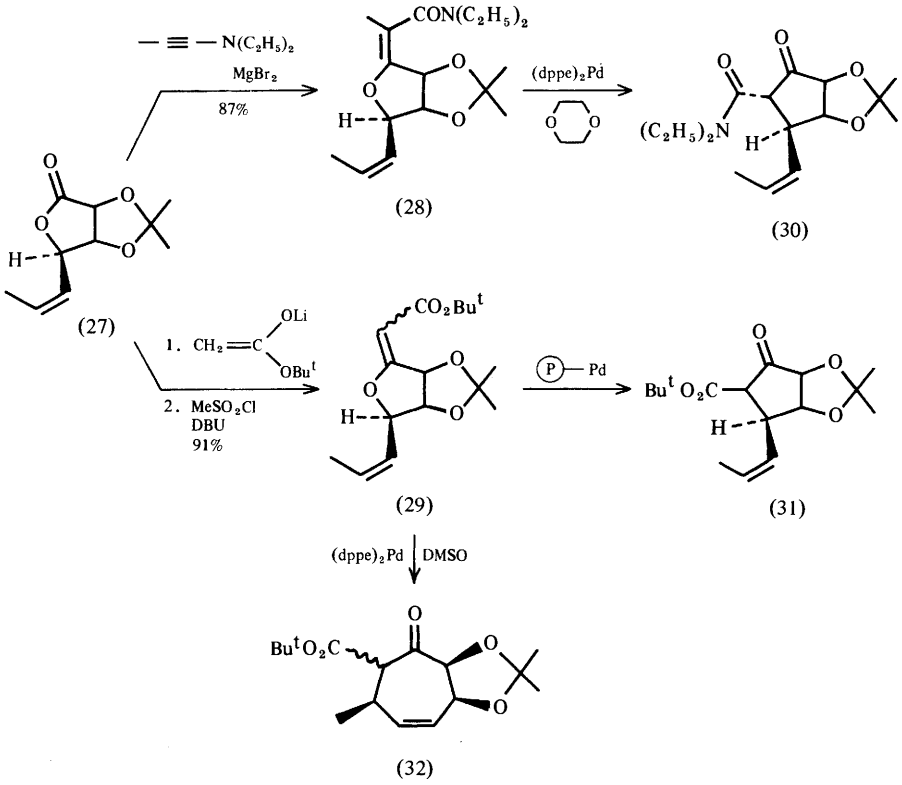
A general cyclopentanone synthesis hinges on the availability of 2-alkylidene-5-vinyltetrahydrofurans.[20] One such route highlights the utility of the 1-arylthiocyclopropane-1-carboxaldehyde as a useful conjunctive reagent for synthesis. A totally different approach *via* the aldehyde (23) as an alternative conjunctive reagent takes cognizance of the potential of an intramolecular Michael addition of an alcohol onto an ynoate, *i.e.* (24) → (25). Simple base catalysed addition was unsatisfactory. On the other hand, sodium benzenesulphinate proved to be an exceptionally efficient nucleophilic trigger that permitted obtention of the requisite substrates in excellent yields. Palladium-initiated




[20] B. M. Trost and T. A. Runge, *J. Am. Chem. Soc.*, 1981, **103**, 7559.

isomerization then completes the cyclopentanone synthesis, which in this case generates a prostaglandin intermediate, (26).

A chiral cyclopentanone synthesis emerges from the utilization of lactones that derive from carbohydrates as precursors to 2-alkylidene-5-vinyltetrahydrofurans. Olefination of (27), derivable from D-mannose, proceeded *via* two

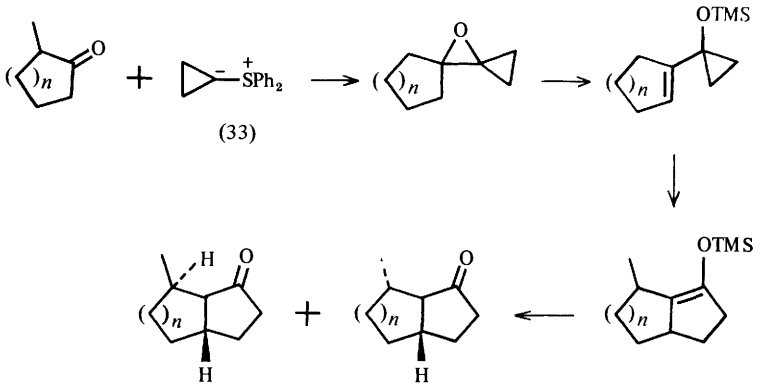



pathways; (*a*) condensation of the lactone with an ynamine[21] in the presence of a Lewis acid to give directly a vinylogous urethane (28), and (*b*) addition of an ester enolate followed by dehydration to give a vinylogous carbonate (29). Subjection of (28) to a soluble palladium(0) catalyst in dioxane leads to the cyclopentanone (30) with faithful translation of the chirality of (28). A similar rearrangement of (29) to cyclopentanone (31) occurred with a polymerically bound palladium(0) catalyst; whereas, the soluble palladium(0) catalyst in DMSO gave the product of [3.3] rearrangement, (32). The ability to orientate the reaction pathway between the [1.3] and [3.3] rearrangements by variation of ligand and solvent should prove generally useful.

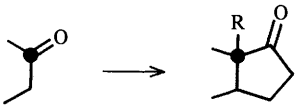
[21] J. Ficini, J. P. Genet, and J. C. Depezay, *Bull. Soc. Chim. Fr.*, 1973, 3367.

**5 Cyclopentanone Annulation *via* a Vinylcyclopropane Rearrangement**

In addition to general cyclization methods, there exist potential routes that are unique for five-membered rings. One of the least appreciated until recently derived from the vinylcyclopropane to cyclopentene rearrangement.[22] The utility of such a method hinges, to a large extent, on the accessibility of the requisite vinylcyclopropane. Diphenylsulphoniumcyclopropylide (33) offers




a simple approach.[23,24] Its adduct with carbonyl partners, an oxaspiropentane, is a highly reactive epoxide, which easily suffers base initiated elimination to form a vinylcyclopropanol. Thermal reorganization of the corresponding trimethylsilyl ether produces a cyclopentene bearing a trimethylsiloxy-group on the double bond, *i.e.* an enol silyl ether of the corresponding cyclopentanone.[25,26] Equation 7 illustrates the overall transformation that permits not only a regio-

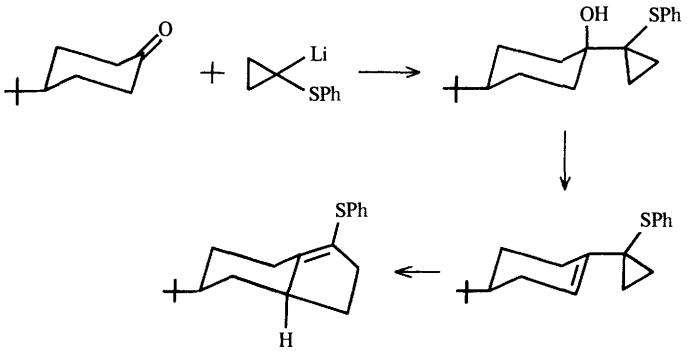



(7)

controlled annulation of the cyclopentanone ring, but also allows for further elaboration of the original carbonyl carbon as a result of the cyclopentanone being initially generated in the form of an enolate equivalent.

A similar annulation emanates from use of the related reagent, 1-lithiocyclopropylphenyl sulphide (equation 8).[27] Dehydration of its carbonyl adduct

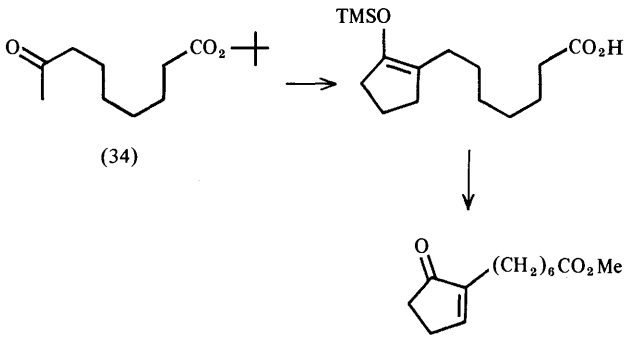
[22] M. R. Willcott, R. L. Cargill, and A. B. Sears, *Prog. Phys. Org. Chem.*, 1972, **9**, 25; J. J. Gajewski, *Mech. Mol. Migration*, 1971, **4**, 7.
[23] B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 1973, **95**, 289, 5311.
[24] P. H. Scudder, Ph.D. Thesis, University of Wisconsin, 1977.
[25] B. M. Trost and P. H. Scudder, *J. Org. Chem.*, 1981, **46**, 506.
[26] Also see J. P. Barnier, B. Garnier, C. Girard, J. M. Denis, J. Salaun, and J. M. Conia, *Tetrahedron Lett.*, 1973, 1747; J. M. Conia and C. Girard, *ibid.*, 1973, 1767; C. Girard, P. Arnice, J. P. Barnier, and J. M. Conia, *ibid.*, 1974, 3329.
[27] B. M. Trost and D. E. Keeley. *J. Am. Chem. Soc.*, 1976, **98**, 248.




(8)

followed by pyrolysis creates a specific enol thioether of the cyclopentanone as a single stereoisomer.

The chemo- and regio-selectivity of this strategy permitted transformation of the ketoester (34) to the prostaglandin intermediate (35).[28] Scheme 3 outlines a retrosynthetic analysis of the novel antitumour compound aphidicolin (36)[29]



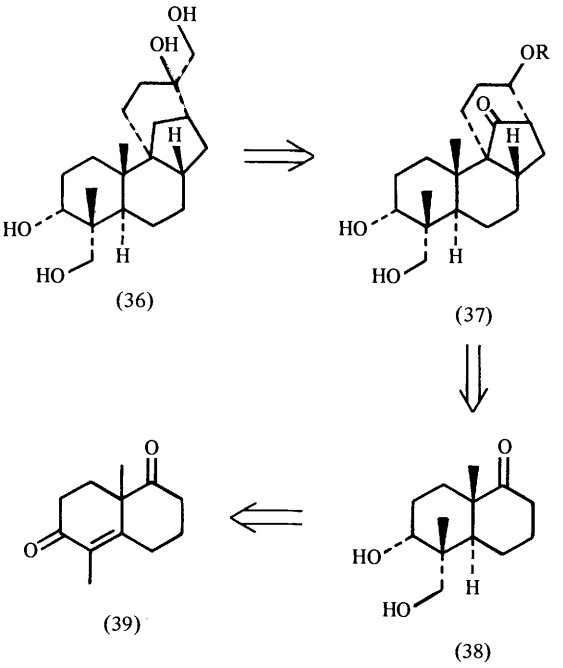

(34)

(35)

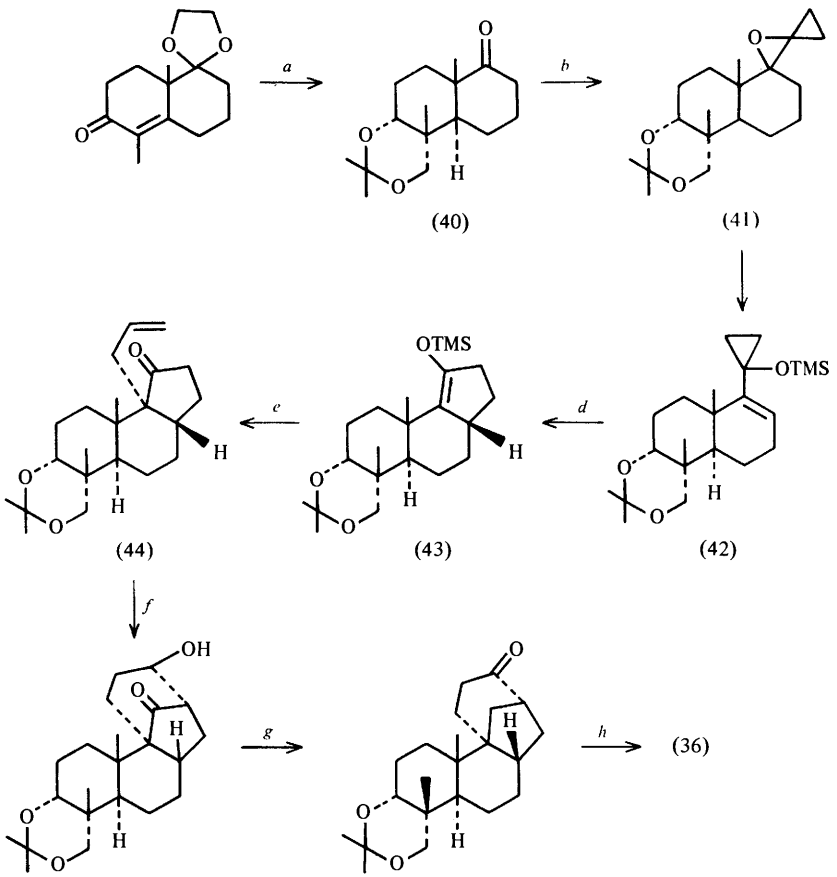
based upon this methodology.[30] From the recognition that standard methodology exists for converting (37) into aphidicolin emerges the definition of this synthesis as a problem in regiocontrolled cyclopentanone elaboration. Thus, by applying the structural interconversion represented in equation 7 to structure (37), this molecule simplifies to (38), which in turn should derive from the common octahydronaphthalenedione (39).

Realization of this plan is summarized in Scheme 4. In the key transformation of ketone (40) to trimethylsiloxycyclopentene (43), the opening of the oxaspiro-

[28] B. M. Trost and S. Kurozumi, *Tetrahedron Lett.*, 1974, 1929.
[29] W. Dalziel, B. Hesp, K. M. Stevenson, and J. A. Jarvis, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2841.
[30] B. M. Trost, Y. Nishimura, and K. Yamamoto, *J. Am. Chem. Soc.*, 1979. **191**, 1328.




**Scheme 3** *Retrosynthetic analysis of aphidicolin*

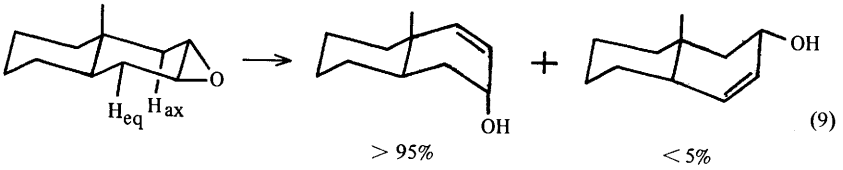



Reagents: (*a*) i, Li, $NH_3$, $Bu^tOH$, THF, TMS—Cl; ii, MeLi, ether, $CH_2O$; iii, $LiBu^i_2Bu^tAlH$, hexane–ether; iv, HCl, $H_2O$, THF; v, MeCOMe, TsOH, 62%. (*b*); (33), DMSO. (*c*): i, PhSeNa, DME; ii, MeC(OTMS)=NTMS, 56% overall for *b* and *c*. (*d*): i, FVP; ii, $Pd(OAc)_2$, MeCN; iii, Li, $NH_3$, THF, $Bu^tOH$ then TMS—Cl, 58%. (*e*); BuLi, THF, HMPA, $CH_2$=$CHCH_2I$, 35%. (*f*): i, $Me_2CHCMe_2BH_2$, diglyme, then NaOH, $H_2O_2$; ii, PCC, NaOAc, $CH_2Cl_2$; iii, KOH, MeOH, 31%. (*g*): i, DHP. TsOH, $CHCl_3$; ii, KOH, $HO(CH_2CH_2O)_3H$; iii, TsOH, MeCOMe; iv, PCC, NaOAc, $CH_2Cl_2$, 62%. (*h*); See Dalziel *et al.* ref. 29

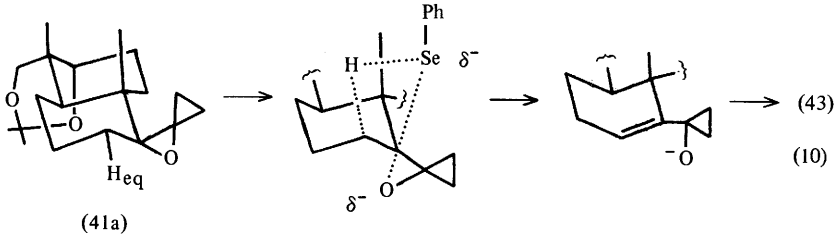
**Scheme 4** *A synthesis of aphidicolin*

pentane required a deviation from the normal base-catalysed process. For simple epoxides, such a reaction involves a *cis syn* elimination preferring removal of an axial proton (see equation 9).[31] In (41) [depicted in (41*a*)], the only hydrogen *cis* to the epoxide oxygen is an equatorial one; indeed, the base catalysed ring opening fails! A simple resolution of this problem derived from

[31] C. L. Kissel and B. Rickborn, *J. Org. Chem.*, 1972, **37**, 2060; R. P. Thummel and B. Rickborn, *ibid.*, 1972, **37**, 3919, 4250; 1971, **36**, 1365.

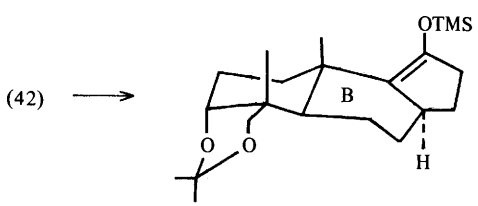



(9)




(41a) (10)

use of a merged substitution–elimination pathway[32] employing phenylselenide anion under aprotic conditions as shown in equation 10. The stereochemistry of the vinylcyclopropane rearrangement of (42) proved equally fascinating. Whereas conformational considerations strongly suggested preferential formation of the desired product (43; $\beta$-H at C-8), experimentally the major product of rearrangement proved to be (44; $\alpha$-H at C-8), in which ring B was



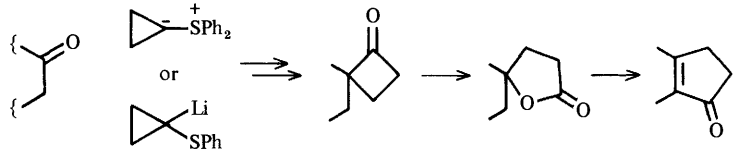

(44)

forced into a boat conformation. Resolution of this stereochemical problem involved obliteration of the stereochemical centre at C-8 by converting the mixture of enol silyl ethers that resulted into the corresponding enone, followed by its reconstitution with the correct $\beta$-H stereochemistry as shown in Scheme 4. With the key ring-structure completed, the remaining stages of synthesis followed more traditional lines as Scheme 4 illustrates.

The cyclopropyl reagents outlined herein offer an alternative cyclopentenone annulation based upon conversion of the initial adducts into spirocyclobutanones.[33] Such strained ketones undergo particularly facile Baeyer–Villiger oxidation to $\gamma$-butyrolactones, which upon subjection to acid, transform to

[32] P. Beltrame, G. Biale, D. J. Lloyd, A. J. Parker, M. Ruane, and S. Winstein, *J. Am. Chem. Soc.*, 1972, **94**, 2240.
[33] B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 1973, **95**, 5321.

cyclopentenones (equation 11).[34] This sequence proved to be a critical elaboration in the synthesis of dodecahedranes.[35]

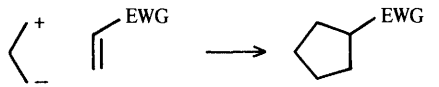



(11)

## 6 A Cycloaddition Strategy

Although cyclization by single bond formation represents a major entry into any ring system, the merit of a cycloaddition strategy provides strong impetus for development of such approaches. The power of the Diels–Alder reaction, whose pre-eminence as a six-member ring forming method becomes increasingly clearer, induces its exploitation for both six-membered and non-six-membered natural products by adjustment of ring sizes or other clever manipulations of Diels–Alder adducts.[36] An analogue of the Diels–Alder reaction, shown in its barest essentials in equation 12, for five-membered ring formation is stated in equation 13. Although 1,3-dipolar cycloadditions for heterocycles are already


(12)




(13)

ingrained in our dictionary of strategies, such an approach for five-membered carbon rings remains elusive.

Trimethylenemethane (TMM), a species well-studied from a physical perspective,[37] offers many synthetic attractions. In addition to providing the requisite ring-system, it provides a functional group of sufficient flexibility that a diverse range of structural types would be approachable. Its absence as a synthetic method stems from the lack of suitable methods for its generation and the low yields of its 'cycloadditions.'[38]

(14)

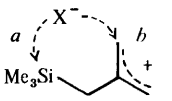
[34] P. E. Eaton, G. F. Cooper, L. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, 1972, **37**, 1947.

[35] L. A. Paquette and D. W. Balogh, *J. Am. Chem. Soc.*, 1982, **104**, 774.

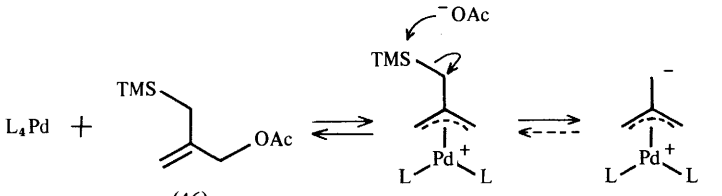
[36] For a recent elegant example, see M. Demuth, P. R. Raghavan, C. Carter, K. Nakano, and K. Schafner, *Helv. Chim. Acta*, 1980, **63**, 2434; W. C. Still and M.-Y. Tsai, *J. Am. Chem. Soc.*, 1980, **102**, 3654.

[37] P. Dowd, *Acc. Chem. Res.*, 1972, **5**, 242; J. A. Berson, *ibid.*, 1978, **11**, 446.

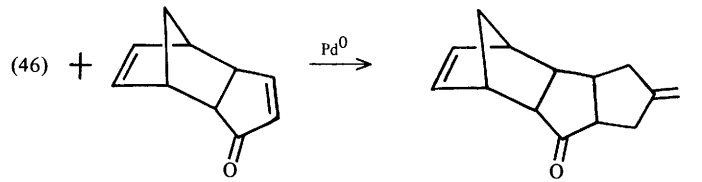
[38] For some elegant recent examples of substituted systems see R. D. Little, G. W. Muller, M. G. Venegas, G. L. Carroll, A. Bukhari, L. Patton, and K. Stone, *Tetrahedron*, 1981, **37**, 4371: R. D. Little and G. W. Muller, *J. Am. Chem. Soc.*, 1981. **103**, 2744; R. D. Little and G. L. Carrol, *Tetrahedron Lett.*. 1981. **22**. 4389.




(45)




(46) (47)




(48) (49)

In circumventing the perceived problems of TMM, a mild method for its generation from readily available precursors as well as a more selective reactivity towards cycloaddition are required. The propensity of silicon to transfer to a silylophile when bound to an electronegative carbon raised the possibility of the desilylation of an intermediate such as (45). The propensity of any silylophile to effect a desilylation [path *a* in (45)] compared to simple charge neutralization [path *b* in (45)] suggested decreasing the probability of the latter pathway by delocalizing the positive charge or, even better, making such a pathway totally reversible. Palladium(0) initiated ionization of (46) offers both![39] However, TMM itself would not be formed, but rather its palladium complex (47).[40–42]

With the hope that such a species would participate in a cycloaddition, (46) was exposed to a catalytic quantity of a palladium(0) complex in the presence of an ambident trap (48); one possessing a strained electron-rich double bond

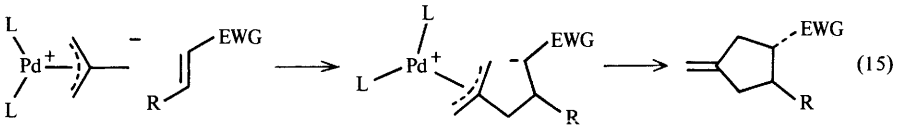
[39] B. M. Trost, *Tetrahedron*, 1977, **33**, 2615; *Pure Appl. Chem.*, 1979, **51**, 787.

[40] For reactions of olefins and alkylidenecyclopropanes catalysed by nickel see R. Noyori, Y. Kumagai, I. Umeda, and H. Takaya, *J. Am. Chem. Soc.*, 1979, **94**, 4018; P. Binger, *Synthesis*, 1973, 427.

[41] For reaction of olefins and alkylidenecyclopropanes catalysed by palladium see P. Binger and U. Schuchardt, *Angew. Chem., Int. Ed. Eng.*, 1977, **16**, 249; *Chem. Ber.*, 1980, **113**, 3334; 1981, **114**, 3313; P. Binger and A. Germer, *ibid.*, 1981, **114**, 3325.

[42] For reaction of trimethylenemethaneiron tricarbonyl see A. C. Day and J. T. Powell, *Chem. Commun.*, 1968, 1241; K. Ehrlich and G. F. Emerson, *J. Am. Chem. Soc.*, 1972, **94**, 2464.

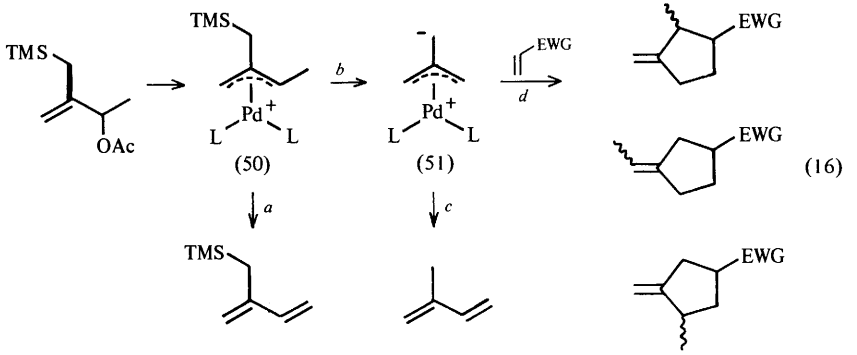
and an electron-deficient one.[43] A single product involving only addition to the electron-deficient double bond, *i.e.* adduct (49), emerged. Equation 15 summarizes




(15)

the general features of the reaction.[44,45] The dipolarophile requires at least one electron-withdrawing group (EWG). The reaction involves a two-step process; conjugate addition of the negative end of the dipole onto the dipolarophile followed by charge neutralization. The degree of stereoselectivity depends upon the rate of the ring closure relative to the rate of bond rotation; in the case of *trans* traps a high selectivity is observed. Among the successful EWG's stand a ketone, an ester, a nitrile, and a sulphone.

The question of the substitution on the dipole determines the full scope of this process. As simple a molecular modification as incorporation of a methyl group is not trivial. As equation 16 emphasizes, several potentially unfavourable

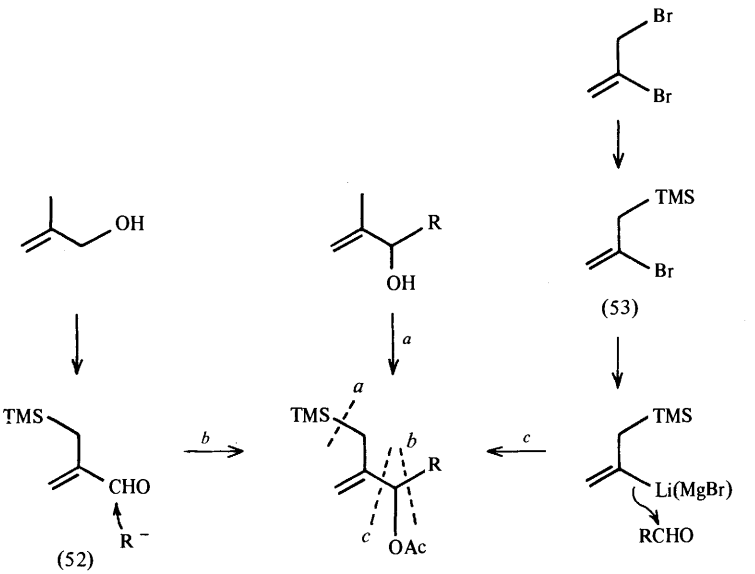



(16)

competitions can doom the desired path. For example, (50) can deprotonate to form a stable molecule (path *a*) or desilylate to form a high energy intermediate (51; path *b*). The latter also can experience a unimolecular hydrogen shift to form isoprene (path *c*) compared to a bimolecular trapping to form the alkylidenecyclopentanes (path *d*). Finally, any cycloaddition can produce a total of six isomers; two stereoisomers each of three regioisomers.

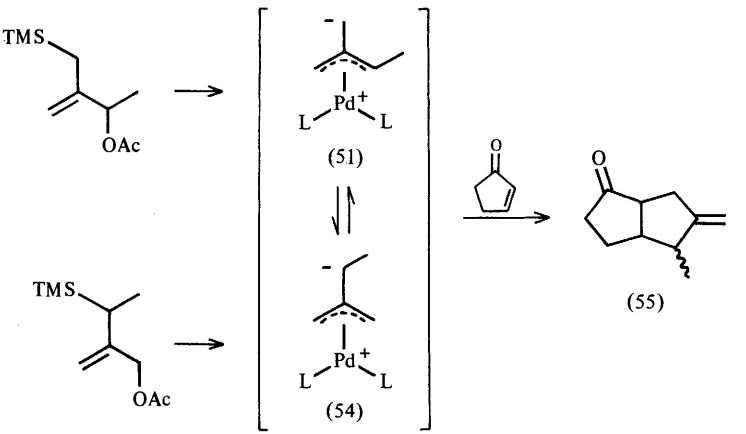
In order to probe such systems, general methods of synthesis need to be developed. Scheme 5 summarizes the three general approaches and introduces

[43] D. M. T. Chan, Ph.D. Thesis, University of Wisconsin, 1982.
[44] B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, 1979, **101**, 6429, 6432.
[45] B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, 1980, **102**, 6359.




**Scheme 5** *Synthetic approaches to silyl alcohols*

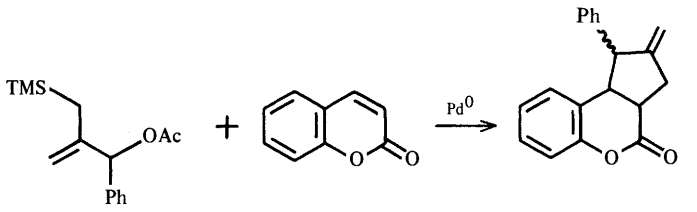
two new bifunctional conjunctive reagents, aldehyde (52)[43] and bromide (53).[46] Path *a* involves the direct metallation with n-butyl-lithium followed by silylation with trimethylchlorosilane. Path *b* envisions (52), which has its origins from methallyl alcohol, as an acceptor reagent requiring a donor reactant. Path *c* reverses the electronic characteristics of the two reacting partners, *i.e.* the silyl component, which has its origins from 2,3-dibromopropene, is the donor reactant.

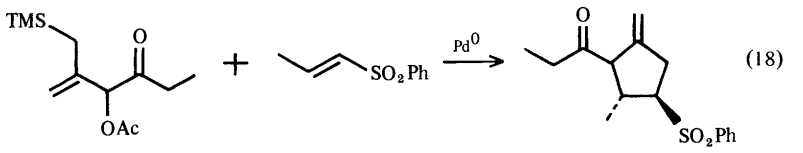


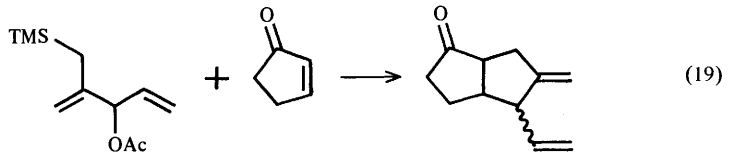

[46] B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, 1982, **104**, in press.

The methyl substituted precursor is prepared by path *a* of Scheme 5.[47] In the event, it participated with a facility equal to the parent system to give a single regioisomer (>20:1), albeit as a mixture of stereoisomers (55) with cyclopentenone. Most strikingly is the location of the methyl substituent in the cycloadduct. To verify that this regiochemistry is independent of the structure of the silyl acetate, an alternative regioisomeric starting material was employed with the same result. In consonance with earlier results, these observations suggest that the intermediate is a rapidly equilibrating pair of TMM–Pd complexes, (51) and (54), and that product formation derives from (54). Fenske–Hall calculations indicate that (54) is more stable than (51).[48] Thus, in contrast to normal intuition, the electron releasing methyl substituent prefers to be on the most electron-rich carbon atom of the TMM–Pd intermediate! Such a reordering of normal organic preferences clearly derives from the effect of the transition metal on chemical reactivity.

$\pi$-Conjugating substituents such as phenyl (equation 17)[43,49] and carbonyl (equation 18)[50] show a similar preference. The case of a vinyl substituent is most curious because of its possible direct participation. Nevertheless, it proceeds without complications (equation 19).[49]

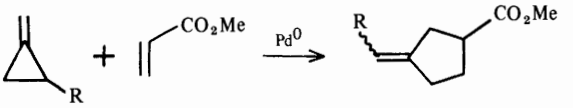


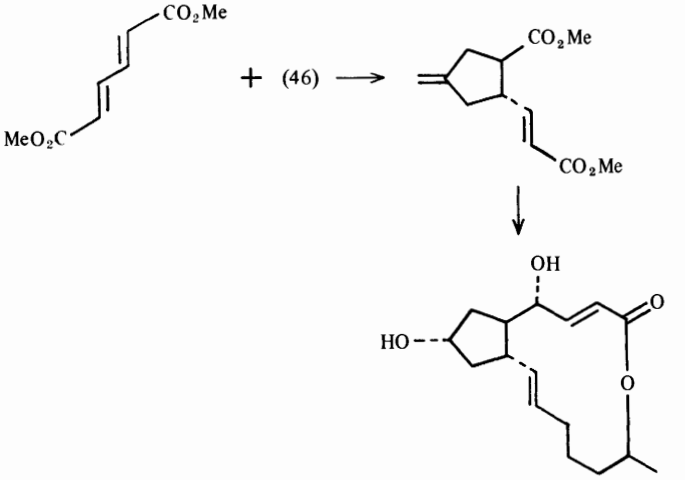

[47] B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, 1981, **103**, 5972.
[48] D. J. Gordon, R. F. Fenske, T. N. Nanninga, and B. M. Trost, *J. Am. Chem. Soc.*, 1981, **103**, 5974.
[49] T. N. Nanninga, unpublished results in these laboratories.
[50] T. Satoh, unpublished results in these laboratories.

It is appropriate to contrast these observations with the palladium catalysed condensations of alkylidenecyclopropanes with olefins.[41] Although it is tempting to interpret the two reactions as proceeding through the same intermediates, many differences are noted; one of the most striking being a different regioisomeric result (equation 20).

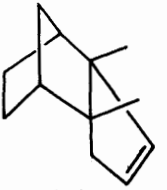



(20)

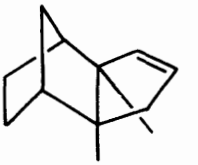
The potential for simplification of synthetic strategy appears exciting. For example, the adduct with dimethyl (*E,E*)-muconate has a striking similarity to




the antitumour macrolide, brefeldin A. Albene, originally assigned structure (56), for which a Diels–Alder strategy would be obvious,[51] had its structure revised to (57),[52,53] for which such a strategy was clearly less satisfactory. On the other



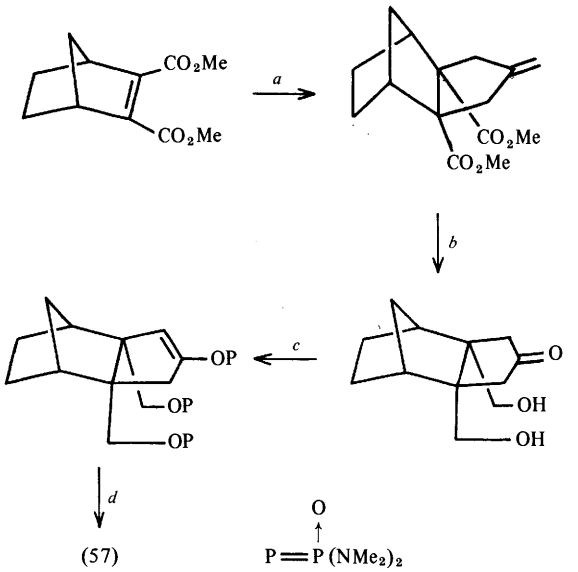
(56)



(57)

[51] K. Vokac, Z. Samek, V. Herout, and F. Sorm, *Tetrahedron Lett.*, 1972, 1665; P. T. Lansbury and R. M. Boden, *ibid.*, 1973, 5017.
[52] W. Kreiser and L. Janitschke, *Chem. Ber.*, 1979, **112**, 408; W. Kreiser, L. Janitsche, W. Voss, L. Ernst, and W. S. Sheldrick, *ibid.*, 1979, **112**, 397.
[53] J. E. Baldwin and T. C. Barden, *J. Org. Chem.*, 1981, **46**, 244.

hand, the normal bias for norbornenes to undergo *exo* addition would make this cycloaddition approach much more likely. Scheme 6 summarizes the

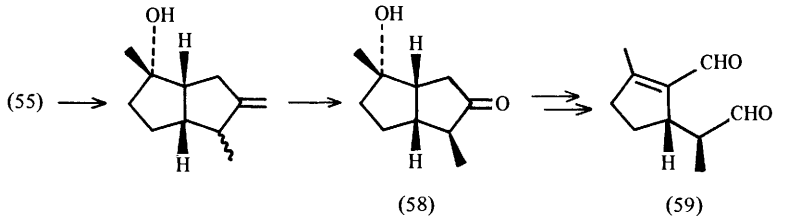



Reagents: (*a*); (46), $(Pr^iO)_3P$, $Pd(OAc)_2$, THF. (*b*): i, LAH, ether; ii, $O_3$, $CH_2Cl_2$, MeOH. (*c*); $KN(TMS)_2$, DME, HMPA, $[Me_2N]_3P(O)Cl$. (*d*); Li, $EtNH_2$, $Bu^t$ OH

**Scheme 6** *A synthesis of* (±) *albene*

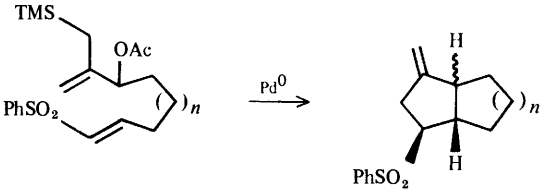
realization of this approach, which permits a five-step synthesis in an overall yield of 21%.[54]

The substituted analogues also have potential applications. For example, the methyl substituted adduct (55) undergoes chemoselective addition of methyllithium, ozonolysis of the exocyclic methylene group, and base equilibration of the secondary methyl group to produce (58),[47] a known precursor[55] of chrysomelidial (59), a constituent of the defensive secretion of the chrysomelide beetle.




[54] P. Renaut, unpublished work in these laboratories.
[55] K. Kon and S. Isoe. *Tetrahedron Lett.*. 1980, 3399.

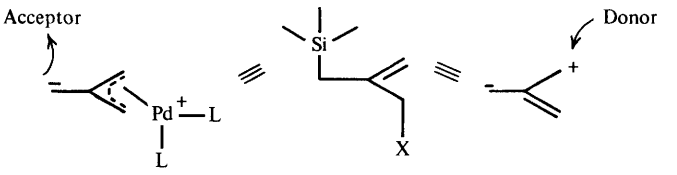
A loganin synthesis from (55) can also be envisaged.[56] Bicyclic systems (60; $n$ = 1 or 2) result from intramolecular versions of this process.[46]




(60)

**7 An Electrophilic TMM Equivalent**

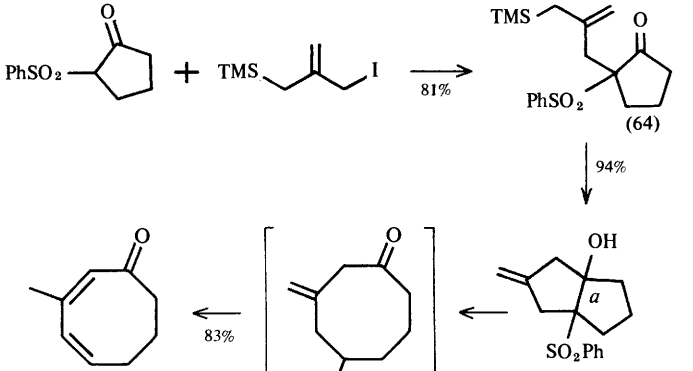
The palladium-catalysed reactions of the silyl alcohols represent a type of behaviour initiated by a nucleophilic TMM partner [*i.e.* (61)]. Equally versatile




(61) (63) (62)

would be a reverse reactivity profile as represented in (62). In fact, such a reactivity is even simpler to envisage since it only requires a selection of X in (63) such that it is sufficiently reactive to be displaced by a nucleophile, but sufficiently unreactive such that (63) does not undergo self-annihilation.

This balance is achieved with (63; X = I) in that it reacts quite smoothly with anions such as that derived from 2-phenylsulphonylcyclopentanone to give (64),

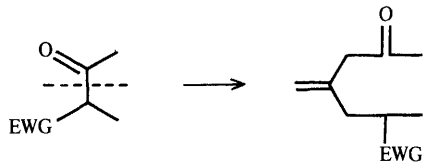



(67) (66) (65)

(64)

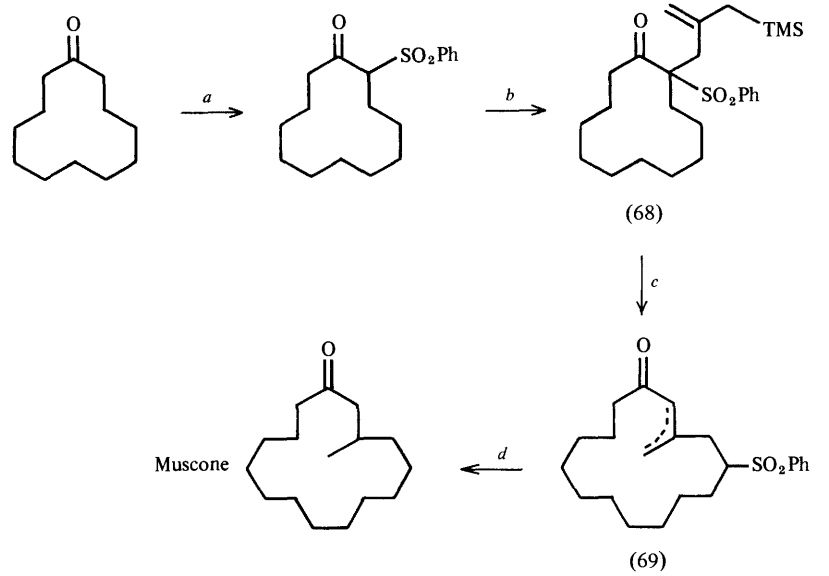
[56] K. Kon and S. Isoe. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 23rd*, 1980, 49.

which in turn can be induced to cyclize to the methylenecyclopentane (65) by unmasking the anion portion of the system with fluoride ion.[57] Strategic placement of the anion stabilizing phenylsulphonyl group and the electron donating hydroxy-group weakens bond '*a*' such that treatment with potassium hydride initiates cleavage of this bond to give, presumably *via* (66), cyclo-octadienone (67). The overall sequence constitutes a three-carbon intercalation between a carbonyl carbon and an α-carbon atom as represented in equation 21. Applied to




(21)

cyclododecanone, this sequence provides an extraordinarily efficient approach (62% overall yield) to muscone (Scheme 7). In the fluoride activation of the



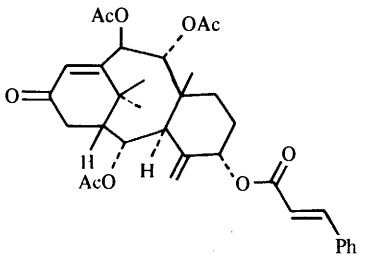

Reagents: (*a*): i, $Br_2$, $CHCl_3$; ii, $PhSO_2Na$, $(C_6H_{13})_4NBr$, DMF, 85%. (*b*): NaH, DME, (63; X = I), 83%. (*c*); $Bu_4NF$, THF, 92%. (*d*): i, $H_2$, 5% $Pd/BaSO_4$. EtOH; ii, 6% Na/Hg. $Na_2HPO_4$, MeOH, 95%

**Scheme 7** *A synthesis of muscone*

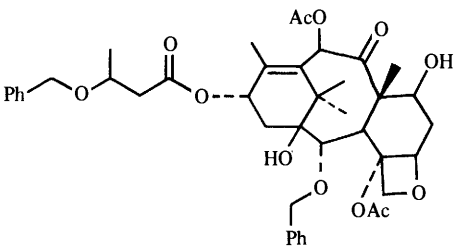
[57] B. M. Trost and J. E. Vincent, *J. Am. Chem. Soc.*, 1980, **102**, 5680.

allylsilane (68), the intermediate methylenecyclopentane is not observed, the direct product being the ring enlarged (69).

Such an approach provides a potential solution to the taxane family as represented by taxinine (70) and taxol (71).[58] The bicyclo[5.3.1]undecane skeleton

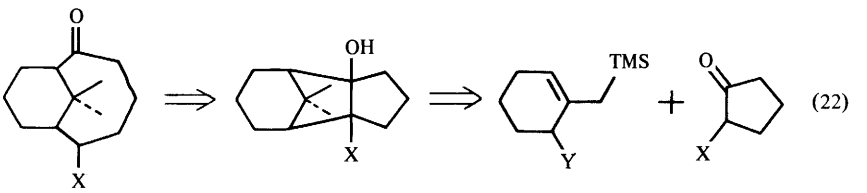


(70)



(71)

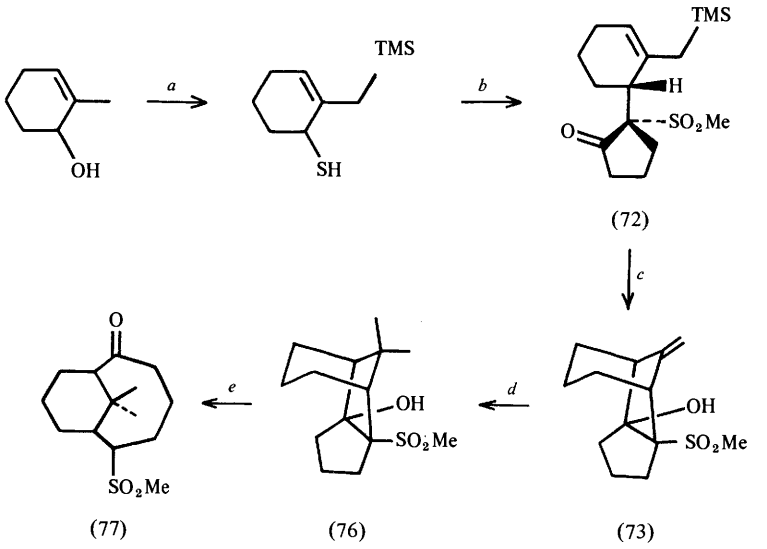
bearing a *gem* dimethyl group embedded in the centre of the ring system can be analysed *via* this type of intercalation procedure as shown in equation 22.



(22)

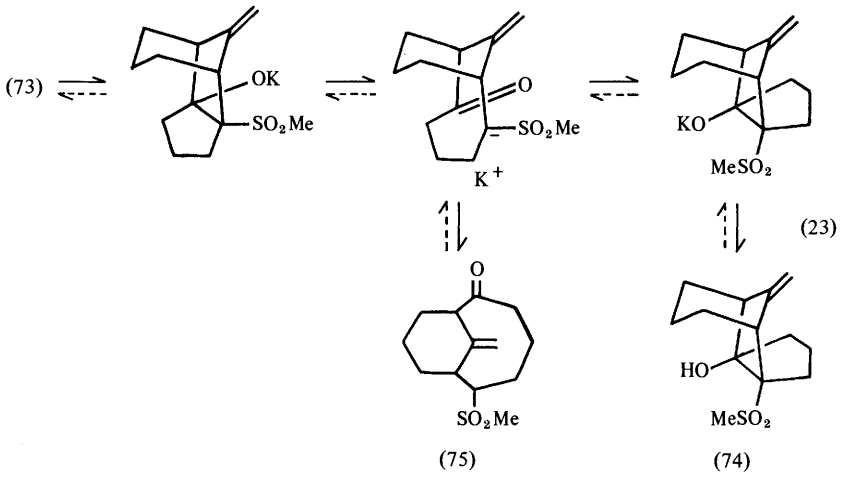
2-Methyl-3-hydroxycyclohexene silylates selectively at the methyl group which then, by a series of [3.3] and [2.3] sigmatropic rearrangements, leads directly to the cyclization precursor (72; Scheme 8).[59] Whereas, fluoride induced cyclization failed, Lewis acid initiated cyclization produced the methylenecyclopentane analogue (73). Its fragmentation proved most instructive (equation 23). Treatment of (73) with potassium hydride in DME followed by protonation led *via* only *endo–exo* interconversion into (74). On the other hand, a mixture of (74) and (75), which ranged from 1:1 to 1:9, resulted by addition of 18-crown-6 and [2.2.2]cryptand respectively. As implied by equation 23, these observations are nicely accommodated by the dependency of the equilibria among the salts on the structure of the ion pairs, which permits an extraordinary level of control. On the other hand, equilibrating the neutral hydrocarbons by simply using a catalytic amount of potassium t-butoxide in DMSO converted (73) exclusively into the ring enlarged (75). As shown in Scheme 8, application of this latter procedure to (76), which derives from (73), smoothly generates the bridged bicyclic portion of the taxanes.

[58] R. W. Miller, *J. Nat. Prod.*, 1980, **43**, 425.
[59] B. M. Trost and H. Hiemstra, *J. Am. Chem. Soc.*, 1982, **104**, 886.

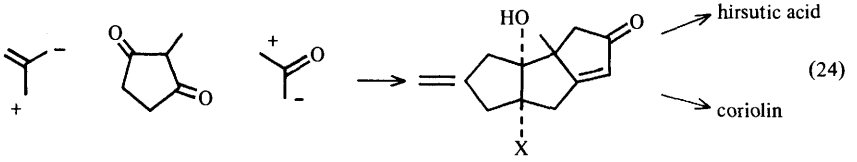



Reagents: (*a*): i, BuLi, ether, TMS—Cl; ii, NaH, $CS_2$ then MeI; iii, $\Delta$; iv, LAH, ether, 38%. (*b*): i, 2-chlorocyclopentanone, NaH, DMF; ii, KH, DME, $\Delta$ then MeI; iii, MCPBA, $CH_2Cl_2$, $NaHCO_3$, 41%. (*c*); $EtAlCl_2$, PhMe, 73%. (*d*): i, $Et_2Zn$, $CH_2I_2$, PhH, air; ii, $H_2$, $PtO_2$, NaOAc, HOAc, 81%. (*e*); cat $Bu^tOK$, DMSO, 95%

**Scheme 8** *A synthesis of a taxane model*




Although the application of this electrophilic synthon of TMM for three-carbon intercalation is clearly promising, it also permits evolution of efficient strategy towards polycylic cyclopentanoid natural products. For example, (78),




(24)

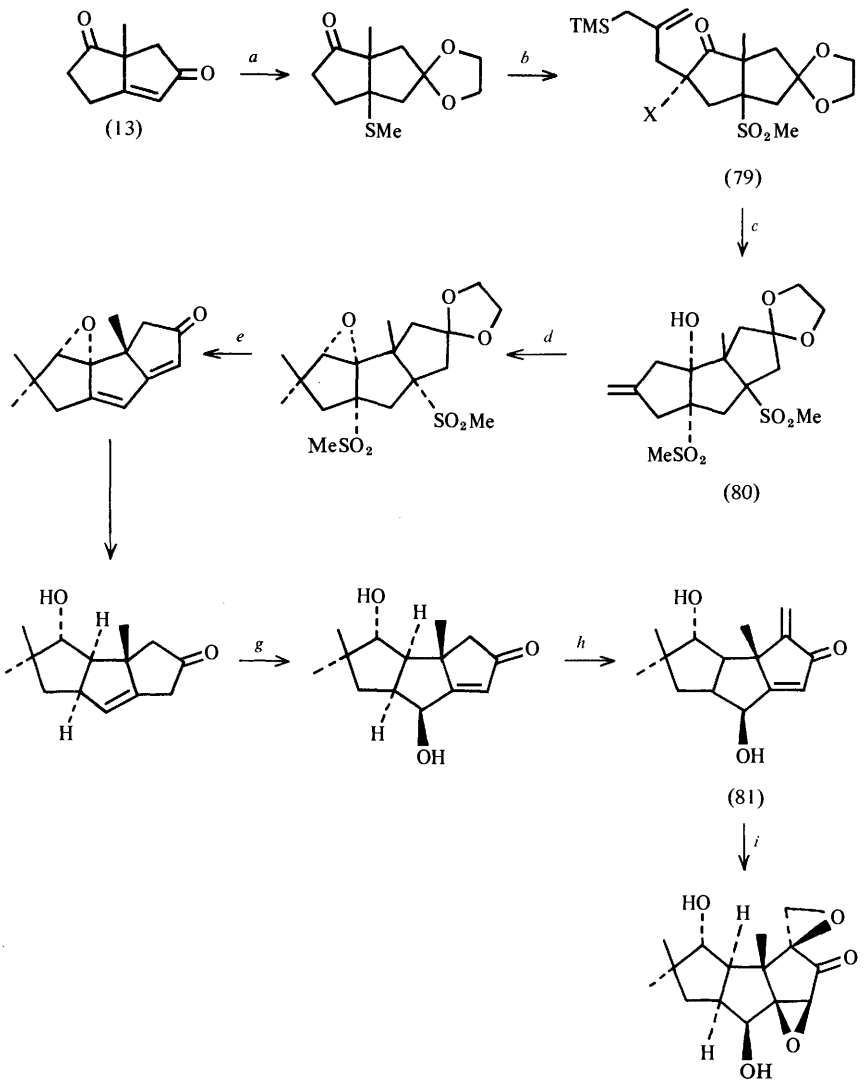
(78)

which may derive from a synthon for an oxatrimethylenemethane as well as the electrophilic version of trimethylenemethane alluded to herein condensing with 2-methylcyclopentan-1,3-dione, can be envisaged to be a common precursor to both hirsutic acid and coriolin. As detailed earlier, 2-ethoxyallyl acetate serves nicely as a synthon for oxatrimethylenemethane in providing ready access to bis-nor-Wieland–Miescher ketone (13).[13,15] The next annulation required the introduction of a substituent that would serve as a stereochemical anchor, *i.e.* a substituent that would fix the stereochemistry of a third five-membered ring and be easily dismissed once its mission was accomplished. An alkylthio-group nicely served this purpose as detailed in Scheme 9 since (79; X = H) showed a propensity to isomerize.[60] Introduction of the methylene-cyclopentane ring was best achieved by alkylating the $\beta$-ketosulphide with (63; X = I) but by cyclizing the $\beta$-ketosulphone. Tricycle (80) provides a convenient divergence point to either hirsutic acid or coriolin, the latter being the most complicated member of the hirsutane family.[61] Choosing coriolin as the target, the exocyclic methylene group simply becomes a *gem* dimethyl group *via* cyclopropanation and hydrogenolysis. With the remaining structural modifications being mainly adjustment of oxidation level as outlined in Scheme 9, dienone (81), the penultimate intermediate in all the previous syntheses of coriolin,[62] and thus coriolin becomes available using more standard methodology.

## 8 Conclusions

While much attention focuses on medium and large rings, the plethora of biologically significant cyclopentanoids reawakens concerns regarding their synthesis. The fact that viewing synthetic approaches to them as simple extrapolations from methods available to make six-membered rings can be painfully deceptive and that the most powerful method for making six-membered rings does not apply directly to five-membered rings opens the challenge for new methodology. The methods detailed contribute to meeting this challenge.

[60] B. M. Trost and D. P. Curran, *J. Am. Chem. Soc.*, 1981, **103**, 7380.
[61] H. Nakamura. T. Takita, H. Umezawa, K. Mamuru, N. Yuga, and Y. Itaka, *J. Antibiot.*, 1974, **27**, 301.
[62] K. Tatsuta, K. Akimoto, and M. Kinoshita, *J. Antibiot.*, 1980, **23**, 100; S. Danishefsky, R. Zamboni, M. Kahn, and S. J. Etheridge, *J. Am. Chem. Soc.*, 1981, **103**, 3460; M. Shibasaki, K. Iseki, and S. Ikegami, *Tetrahedron Lett.*, 1980, 3587.
[63] H. Hashimoto, K. Tsuzuki, F. Sakan, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, 1974, 3745.




Reagents: (*a*): i, $Et_3N$, MeSH, MeOH; ii, $HOCH_2CH_2OH$, camphorsulphonic acid, PhH, 92%. (*b*): i, KH, MeSSMe, DME; ii, KH, DME, (63; X = I), 57%. (*c*): i, MCPBA, $CH_2Cl_2$, $NaHCO_3$; ii, $Bu_4NF$, THF, 55%. (*d*): i, $Et_2Zn$, $CH_2I_2$, PhH, air; ii, $H_2$, $PtO_2$, HOAc, NaOAc; iii, $SOCl_2$, $C_5H_5N$; iv, MCPBA, $CH_2Cl_2$, 62%. (*e*): i, 10% $HClO_4$, acetone; ii, DBU, $CH_2Cl_2$, 91%. (*f*): i, Na naphthalenide, DME then DBU, $CH_2Cl_2$; ii, Li, $NH_3$. (*g*): i, MCPBA, $CH_2Cl_2$; ii, DBU, $CH_2Cl_2$. 43% overall for *f* and *g*. (*h*): i, $CF_3C(OTMS)=NTMS$, DMF; ii, LDA, THF–HMPA, TMS—Cl; iii, $Me_2NCH_2I$, $CHCl_3$; iv, MeI, ether; v, DBU, $CH_2Cl_2$, 46%. (*i*); As *per* Danishefsky *et al.* ref. 62

**Scheme 9** *A synthesis of coriolin*

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