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L. A. Paquette



Recent Synthetic Developments in Polyquinane Chemistry

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Recent Synthetic Developments in Polyquinane Chemistry

By L. A. Paquette



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Table of Contents

I	Introduction	1
II	New Synthetic Developments	2
	A Annulation Reactions	2
	1 Acid- and Base-Promoted Cyclizations	2
	2 Intramolecular Ylide Additions	5
	3 Weiss-Cook Condensations	7
	4 [3 + 2] Cycloaddition Methodology	8
	5 Silicon-Assisted Ring Closures	10
	6 α -Diazo Ketone Decompositions	12
	B Ring Expansion, Contraction, and Cleavage Processes	12
	C Transannular and Intramolecular Cyclizations	15
	D Rearrangement Routes to Polyquinanes	18
	1 Thermochemical Pathways	18
	2 Carbocation-Based Approaches	21
	3 Base-Promoted Isomerizations	24
	4 Photochemical Reactions	25
	5 Free Radical and Carbenic Avenues	29
	6 Miscellaneous Schemes	29
	E Meta-Photocycloadditions	31
	F Trapping of 1,3-Diyls	32
	G Production of Tri- and Tetraquinanes	33
III	Functional Group Manipulation within Polyquinanes	40
	A Ring Opening of Tricyclo[3.3.0.0 ^{2,8}]octan-3-ones	40
	B Reactions Involving Ketonic Substrates	42
	C Use of Other Carbonyl Functional Groups	47
	D Reactions Involving Olefinic Centers	49
	E Miscellaneous Reactions	54
IV	Spectral Data on Bicyclo[3.3.0]octanes	57
V	Simpler Molecules of Theoretical Interest	58
	A Pentalene	58
	B Semibullvalenes	58

C	Brexanes, Brendanes, and <i>syn/anti</i> -Sesquinorbornanes	62
D	Adamantane Isomers	65
E	Propellanes	68
F	Tricyclo[3.3.0.0 ^{3,7}]octanes	70
G	Fenestranes	71
H	(<i>D</i> ₃)-Trishomocubanes and Congeners	73
I	Triquinacenes and Related Molecules	76
J	Peristylanes	81
VI	Natural Products Chemistry	84
A	Isolation and Physical Properties	84
B	Chemical Transformations	85
VII	Synthesis of Diquinane Natural Products	89
A	Cedranoids	89
B	Gymnomitrol	91
C	Pentalenolactone	95
D	Pentalenolactone E Methyl Ester	96
E	Quadrone.	97
F	Carbaprostacyclins.	102
VIII	Synthesis of Triquinane Natural Products	108
A	Linear Triquinanes.	108
1	Hirsutine	108
2	The Capnellene Group	111
3	Coriolin	114
4	Hirsutic Acid	118
B	Angular Triquinanes	121
1	Isocomene	121
2	Silphinene	124
3	Pentalenene	125
4	Senoxydene	126
5	Pentalenic Acid	127
6	Retigeranic Acid.	128
C	Propellane Structures.	130
1	Modhephene	130
IX	The Quest for Dodecahedrane	135
A	C ₁₆ -Hexaquinacene	135
1	Synthesis and Properties	135
2	Functionalization Reactions.	136
B	Alternative Approach to C ₁₆ -Hexaquinanes	137
C	Peristylenones and Norperistylenones.	139

D C₂-Dioxa-C₂₀-octaquinane 140

E Approaches to Higher Polyquinanes 142

F Pentagonal Dodecahedranes. 143

 1 The 1,16-Dimethyl Derivative 143

 2 Monomethyl Dodecahedrane 145

 3 The Parent C₂₀H₂₀ Hydrocarbon 146

X References. 148

Subject Index 159

Author Index Volumes 101–119 161

I Introduction

By the mid-1970's it had become clear that the area of polyquinane chemistry was on the verge of an explosive growth period. There were several underlying reasons for this surge of interest in molecules whose frameworks featured mutually fused cyclopentane rings. Perhaps the most evident was the realization that little attention had previously been paid to methodology for annulating one five-membered ring to another. The need for suitably efficient protocols of this type was arising on several fronts. On the one hand, new natural products were being isolated, the di- or triquinane skeletons of which had not heretofore been appreciated as biogenetically derivable from farnesyl pyrophosphate or related precursors. Independently and with equal intensity, a growing fascination for the possibly unusual physical and chemical properties of yet unknown spherical compounds such as dodecahedrane was gaining rapid momentum. In addition, many novel polycyclopentanoid alicyclic systems of theoretical interest were awaiting the implementation of ingenious routes to their acquisition in the laboratory.

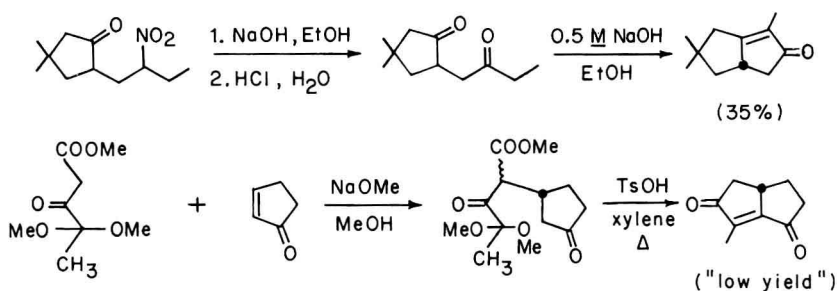
In 1979, we authored a review in *Topics in Current Chemistry* entitled "The Development of Polyquinane Chemistry"⁽¹⁾. Numerous early experimental investigations in this field were surveyed and compiled therein. In the few, short intervening years, the level of research activity dealing with polyquinanes has literally mushroomed. Accordingly, the writing of an updated, complementary review as a means of keeping oneself abreast of the many new and imaginative developments seemed entirely appropriate and even necessary. As before, the intention has been to gather together all relevant new facets of pertinent synthetic methodology in the polyquinane field with a view to stimulating yet more exciting future scientific ventures.

II New Synthetic Developments

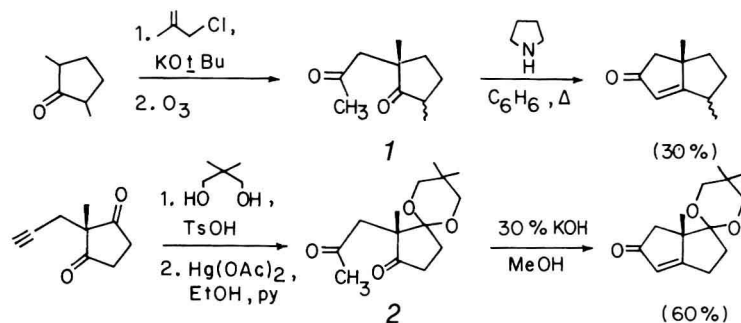
A Annulation Reactions

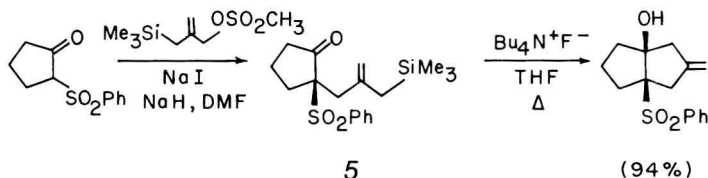
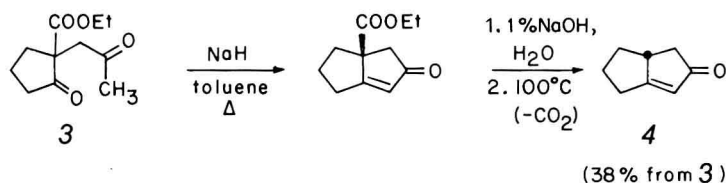
1 Acid- and Base-Promoted Cyclizations

Although bicyclo[3.3.0]octenones lacking angular substituents can be generated under aldol conditions ^{2, 3)}, unsatisfactory yields are commonly encountered. The situation



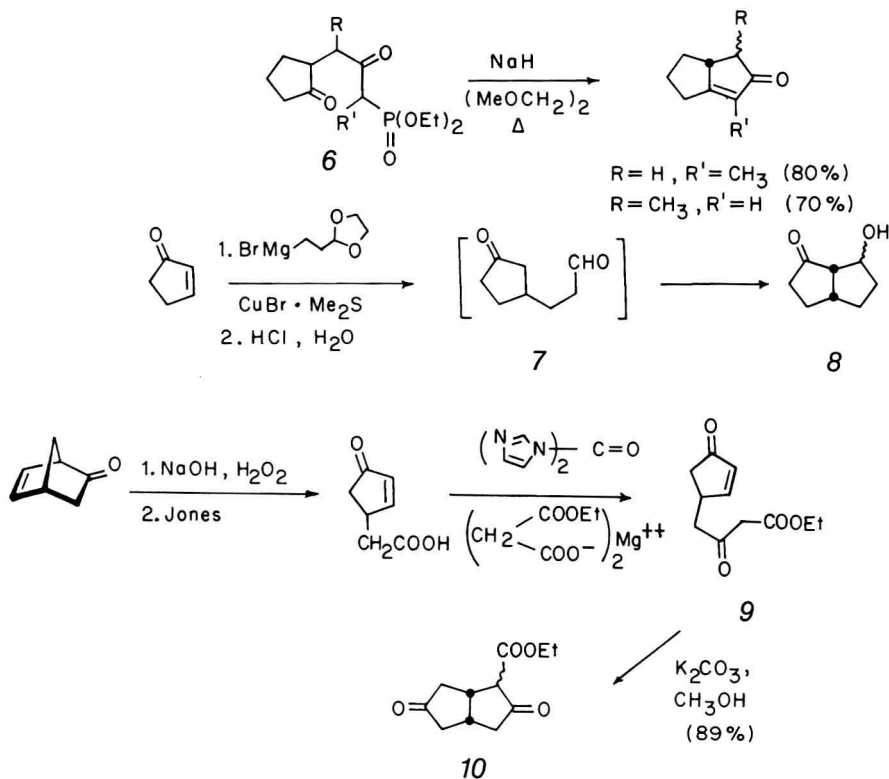
is rather dramatically altered and the process gains considerable preparative respectability when comparable cyclodehydration procedures are applied to suitably substituted analogues (Scheme I). It matters not whether the angular group is alkyl as in **1** ⁴⁾ and **2** ⁵⁾ or electron-withdrawing as in **3** ⁶⁾ and **5** ⁷⁾. Until this phenomenon was recently appreciated, the simple bicyclic enone **4** had eluded synthesis.

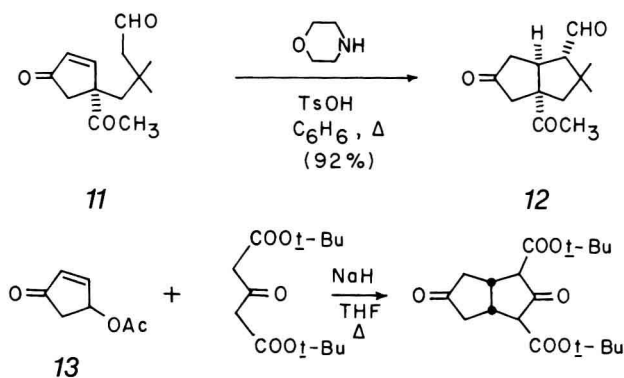




Scheme 1

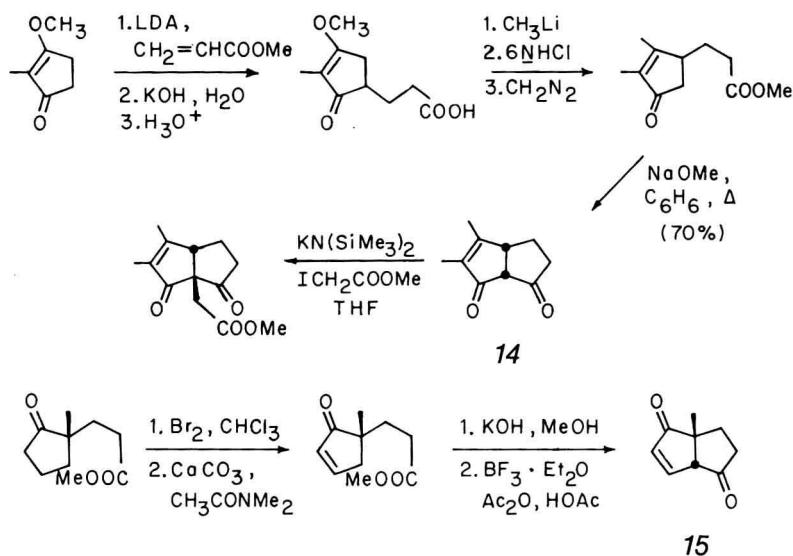
These difficulties can sometimes be surmounted by implementing alternative methodology. Thus, recourse to Wadsworth-Emmons reagents (e.g., 6) has proven generally reliable, although the strongly alkaline conditions required served to dimerize 4 when arrived at in this manner⁸). Annulation also proceeds well when aldolization involves an aldehyde-containing sidechain as in 7⁹). In most instances



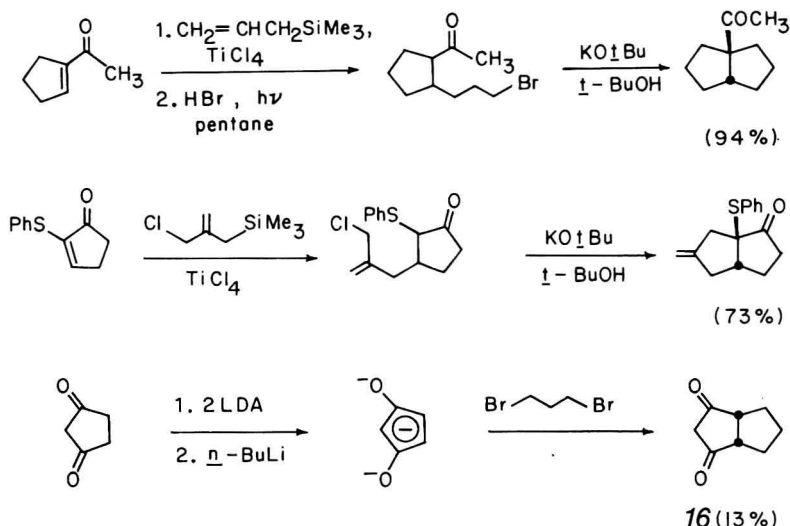


Scheme II

where β -hydroxy ketones of type 8 are formed, dehydration is not spontaneous and requires hydroxyl group activation¹⁰. Although less studied, intramolecular Michael additions exemplified by $9 \rightarrow 10$ ¹¹ and $11 \rightarrow 12$ ¹² give evidence of high efficiency (Scheme II). With 11 in particular, several alternative reaction pathways are possible, and reaction conditions must therefore be closely monitored. The double Michael addition options made possible by 4-acetoxy-2-cyclopentenone (13) are noteworthy.¹³ It would appear on the basis of two reports^{14,15} that intramolecular Claisen condensations have considerable potential in delivering highly functionalized diquinanes (e.g., 14 and 15) not readily available by other means.



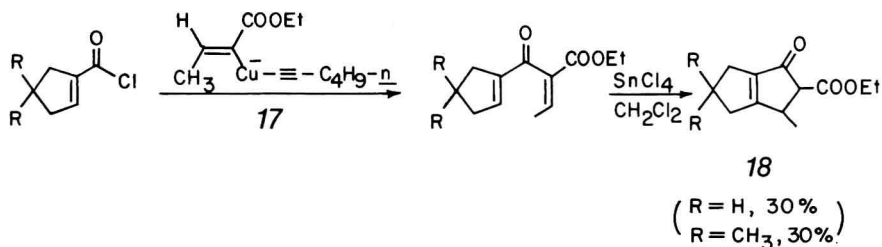
Where alkylation reactions are concerned, the combination of irreversible carbon-carbon bond formation and favorable kinetic considerations frequently provide



Scheme III

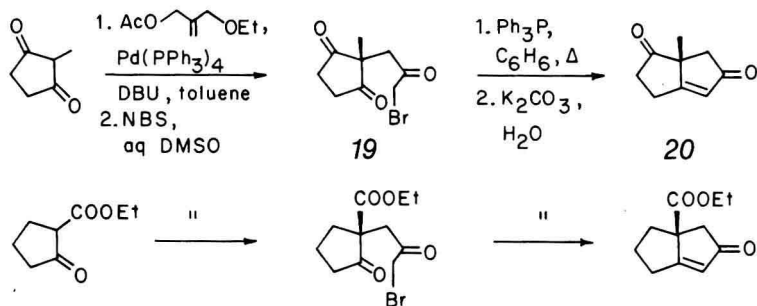
satisfactory product yields (Scheme III).^{16, 17)} The twofold alkylation of the cyclopentane-1,3-dione trianion with 1,3-dibromopropane to provide **16** directly is notable despite the low yield incurred.¹⁸⁾

Finally, Marino and Linderman have shown that the addition of vinylcuprate **17** to cyclopentenylcarbonyl chlorides followed by Lewis acid-promoted Nazarov cyclization is a useful means of gaining access to bicyclic keto esters **18**.¹⁹⁾



2 Intramolecular Ylide Additions

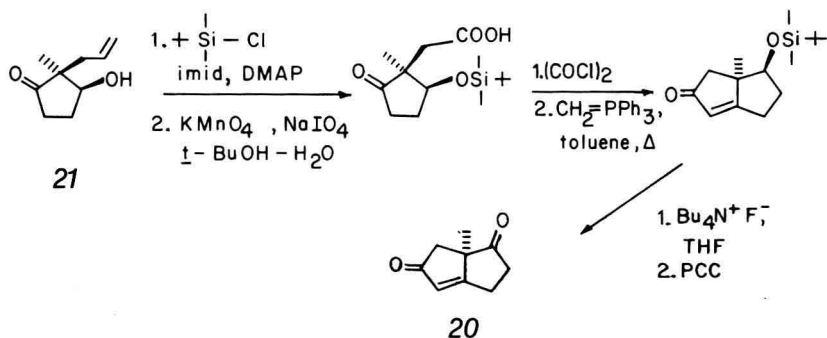
Trost and Curran have developed a cyclopentenone annulation sequence based upon an intramolecular Wittig cyclization which is both general and adaptable to asymmetric synthesis (Scheme IV).²⁰⁾ Palladium(0)-catalyzed reaction of a five-ring β -dicarbonyl system with 2-ethoxy-3-acetoxy-1-propene leads in high yield to the C-alkylated product, which with N-bromosuccinimide is converted to the corresponding α -bromo ketone. Direct conversion to the phosphonium salt, followed by ylide generation at 40 °C, results in cyclization. The formation of **20** in optically active



Scheme IV

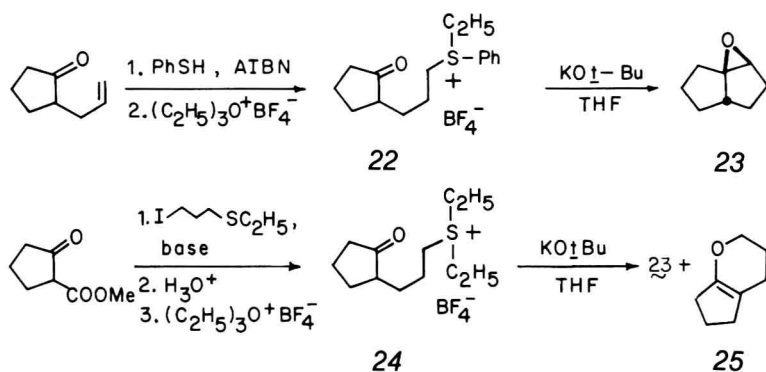
form by condensation of *19* with various optically active phosphines and subsequent exposure to aqueous K_2CO_3 eventuates in poor-to-good chirality transfer (0–77% ee)²¹. A transition state model has been advanced in an effort to rationalize the interdependency of optical induction and phosphine structure.^{20, 21}

In an alternative solution to the problem of obtaining optically active *20*, Brooks and coworkers first subjected *21* (and the corresponding propyl and propargyl derivatives as well) to microbial reduction with baker's yeast²². The resulting ketol (*21*), obtained in greater than 98% enantiomeric purity (the absolute configuration was also established), was subsequently converted in seven steps to enantiomerically pure bis-nor-Wieland-Miescher ketone (*20*, Scheme V).



Scheme V

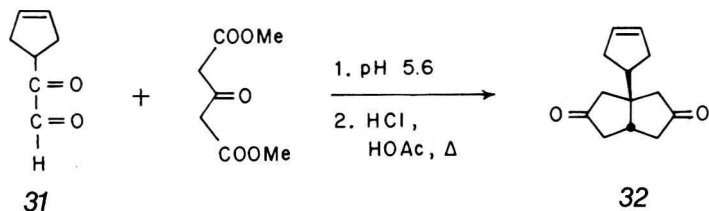
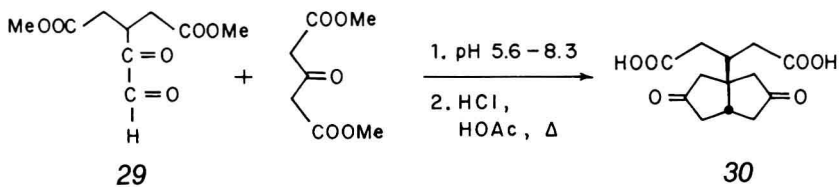
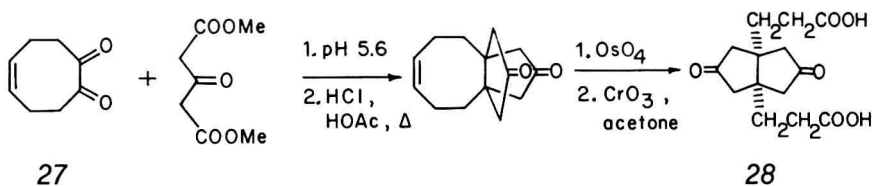
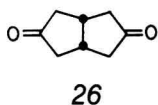
The utility of intramolecular sulfur ylide-carbonyl condensations for achieving cyclopentane epoxyannulation was simultaneously reported by two research groups.^{23, 24} Crandall's approach relies upon regioselective thiophenol addition to 2-allyl-cyclopentanone under free radical conditions and sulfonium salt formation with triethyloxonium fluoroborate (Scheme VI). Under strongly basic conditions, epoxide formation proceeds readily and in good yield. The sulfur substitution plan in *22* appears more suited than that found in *24* since a 1:1 ratio of *23* and *25* is encountered in the last instance.²⁴



Scheme VI

3 Weiss-Cook Condensations

Although Weiss' original study of the condensation of dimethyl 3-ketoglutarate with 1,2-dicarbonyl compounds was made public in 1968,²⁵⁾ it remained for Bertz, Rihs, and Woodward to develop a workable, large-scale laboratory preparation of the parent bicyclo[3.3.0]octan-3,7-dione (26) from glyoxal only last year.²⁶⁾ During the



Scheme VII