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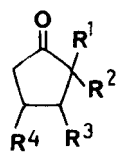
Synthesis of cyclopentanoids—a never ending challenge

Subrata Ghosh* and Debasis Patra

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur Calcutta-700032

Abstract: A novel four-step sequence has been developed for the direct conversion of acyclic and cyclic ketones to vicinally substituted cyclopentanones and spiro cyclopentanones respectively for entry into a wide range of cyclopentanoids. The key step involves a pinacol type rearrangement of alkoxy cyclobutane derivatives involving migration of the stereoelectronically disfavored cyclobutane bond.

A diverse range of cyclopentanoids bear cyclopentane rings of the general structure 1 having substituents on two or three contiguous centres as exemplified by the terpenoids 2-7 (1-5). The synthesis of cyclopentanoids remains a never ending formidable task (6) due to lack of availability of a general method for constructing appropriately substituted cyclopentane rings (7).Our preliminary work on the development and application of a



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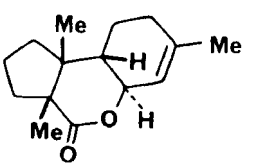

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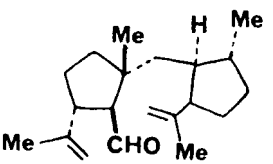

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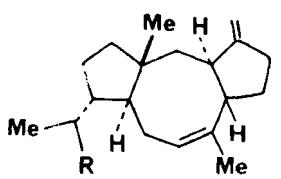

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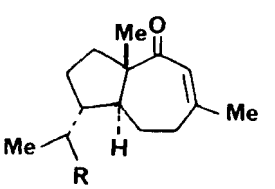
R=(CH2)2CH:C(Me)CH2OH



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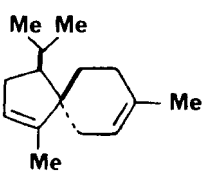
R=CH2COCH2CHMe2



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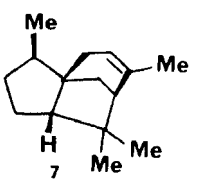

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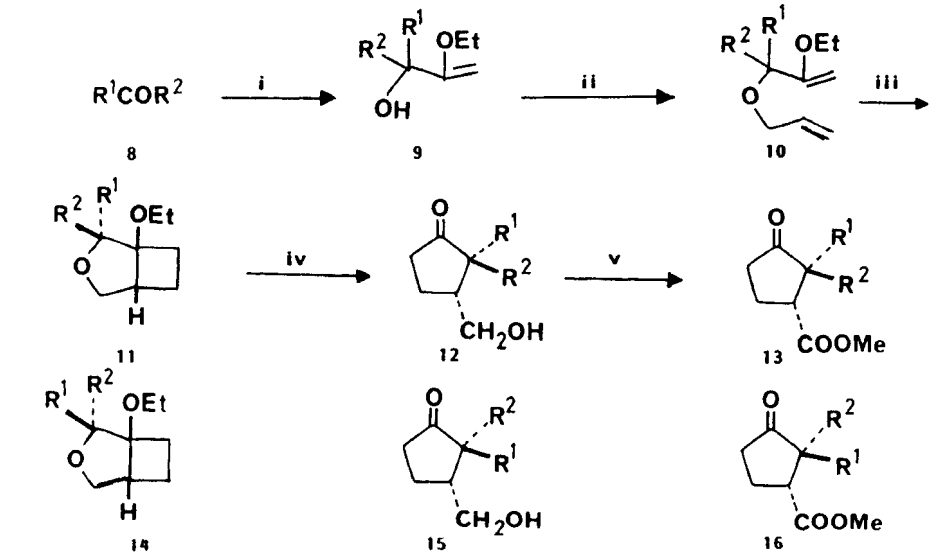
novel strategy that allows synthesis of both substituted cyclopentanones and spiro cyclopentanones from acyclic and cyclic ketones respectively are presented here.

The strategy is illustrated by transformation (8) of diethyl ketone 8a to the substituted cyclopentanone 12a (Scheme-1). Reaction of diethyl ketone 8a with ethoxyvinyllithium afforded the carbinol 9a. The carbinol 9a was then converted to the diene 10a. Photoirradiation of the diene 10a in presence of CuOTf as catalyst afforded in very good yield the cyclobutane derivative 11a.Treatment of the adduct 11a with TfOH effected smooth rearrangement of the cyclobutane ring to produce the cyclopentanone derivative 12a arising by migration of the C_1-C_5 bond. Using this sequence

acetone **8b** was transformed (9) to the known cyclopentanone derivative **12b**, an advanced intermediate in the synthesis (10) of planococcyl acetate, the pheromone of citrus mealy bug. The four-step synthesis of the cyclopentanone derivative **12b** compared to its reported eleven-step synthesis demonstrates the efficiency of the present synthetic protocol.



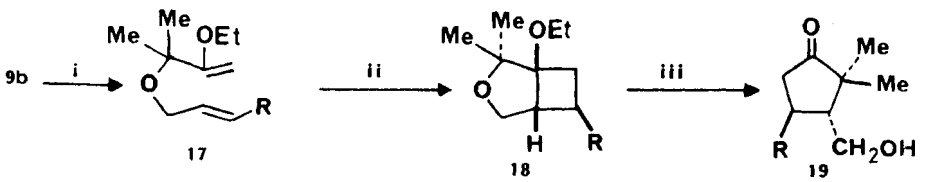
	a	b	c	d	e	f	g	h
R^1 =	Et	Me	Me	Me	Me	Me	Me	H
R^2 =	Et	Me	Et	CH_2CH_2Ph	CH_2Ph	4-methyl cyclohexyl	1,4-dimethyl cyclohexyl	$CHMe_2$

Scheme 1 : Reagents and Conditions : i, Bu^tLi, ethyl vinyl ether, THF, -70°C to rt; ii, NaH-THF, allyl bromide, HMPA, reflux; iii, $h\nu$, Et_2O, CuOTf; iv, TfOH, CH_2Cl_2, -78°C to rt; v, Jones reagent, acetone, 0°C to rt then CH_2N_2,

In case of unsymmetrical ketones, the size of the substituents had profound influence on the stereochemical outcome of the cycloaddition (11).This was reflected in the gradual increase in the ratio (3.8 to 5 to 19 to >99) of the photoadducts **11c-g** and **14c-g** with increasing size of the group from Et to CH_2CH_2Ph to CH_2Ph to 4-methyl cyclohexyl. Rearrangement of the cyclobutanes **11c-g** and **14c-g** was found to be totally stereospecific to produce respectively the cyclopentanone derivatives **12c-g** and **15c-g**. The noteworthy feature in this strategy is the easy stereoselective synthesis of the otherwise difficultly accessible cyclopentanone derivatives **12f** and **12g**, the carbon skeleta of cuprenolide and trichodiene. However, this route failed to convert aldehydes eg. **8h** to the cyclopentanone **12h** as the photoadduct **11h** was totally resistant to acids.

This protocol was found to be extremely efficient for stereoselective synthesis of cyclopentanones with three contiguous substituents (**Scheme-2**). The dienes **17a** and **17b** prepared from the carbinol **9b**, afforded the photoadducts **18a** and **18b** along with their other diastereoisomers in 3:1 and 4:1 ratios respectively. Rearrangement of the photoadduct mixture obtained from **17a** led to the substituted cyclopentanone derivative **19a** along with its other diastereoisomer. The phto-adduct mixture obtained

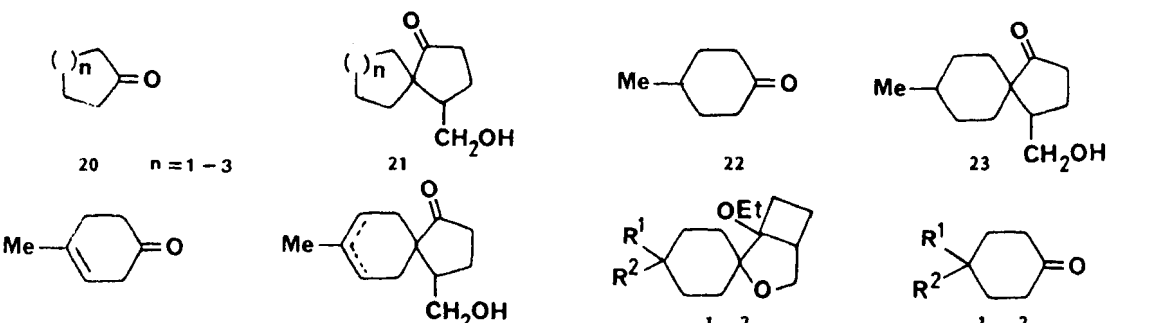
from the diene **17b** before rearrangement, was transformed to the thermodynamically more stable ester **18c** (12). The cyclobutane ring in **18c** underwent smooth rearrangement to produce exclusively the cyclopentanone derivative **19c** in excellent yield.



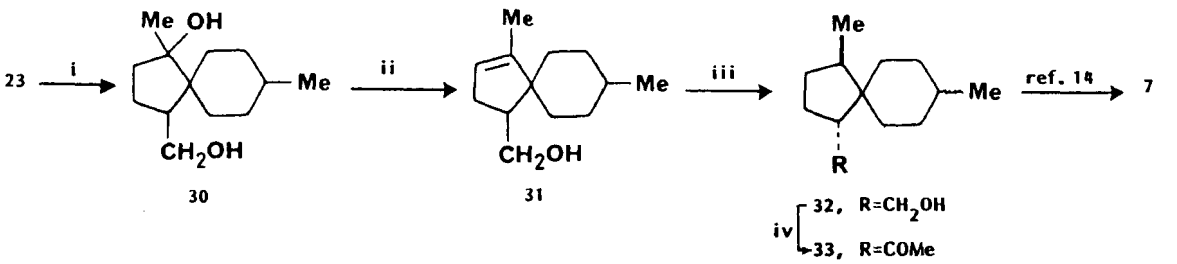
a, R=Me; b, R=CH:CHMe; c, $R=CO_2Me$

Scheme - 2 Reagents and Conditions : i, NaH-THF, crotyl bromide (for a), MeCH:CHCH:$CHCH_2Br$ (for b), HMPA, reflux; ii, $h\nu$, Et_2O, CuOTf; iii, TfOH, CH_2Cl_2 (for a), OsO_4-$NaIO_4$-Et_2O, H_2O then Jones reagent acetone and then CH_2N_2, Et_2O (for b).

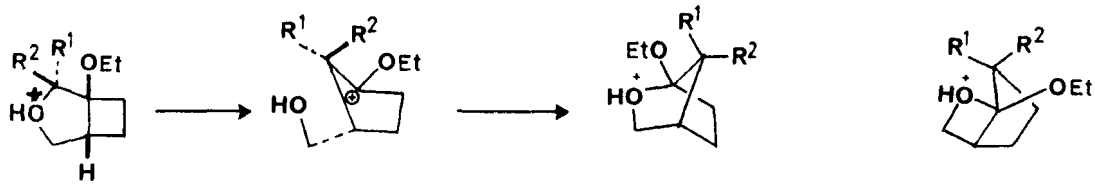
The greatest advantage of this protocol is its application in the synthesis of spiro cyclopentanones.A number of cyclic ketones **20a-c**,**22**,**24** was converted to the spiro cyclopentanones **21a-c**, **23** and **25** respectively in overall good yield (13). Cyclic diones can also be used as demonstrated by transformation of the mono protected ketone **26** to the spiro cyclopentanone **25** through the photoadduct **27** after deketalisation, MeLi addition and



rearrangement of the resulting cyclobutane **29**. The spiro cyclopentanone **25** is suitably functionalised for elaboration to acoranes and cedranes. Using this strategy a formal synthesis of α-cedrene has been accomplished (**Scheme-3**)(13).



Scheme-3 : Reagents and Conditions : i, dihydropyran, PPTS, CH_2Cl_2; MeLi, THF, reflux; PPTS, MeOH; ii, DMSO, 165 °C; iii, H_2, PtO_2, EtOH; iv, Swern oxidation; MeLi, Et_2O; Jones reagent, acetone.



34 35 36 37

Scheme - 4

The selectivity observed in the pinacol rearrangement of the cyclobutane derivatives 11 involving exclusive migration of the C_1-C_5 bond in contrast to the stereoelectronically favoured(15) C_1-C_7 bond is interesting. The origin of this unusual selectivity in bond migration is attributed as follows (Scheme-4). A concerted migration of the C_1-C_5 bond in the protonated species 34 leads to the formation of the cation 35 which is stabilised by the OH group through formation of the cyclic transition state 36. Rapid collapse of 36 leads to the products 12. In case of C_1-C_7 bond migration,the stabilisation of the cation by OH group requires unfavourable formation of the strained oxetane 37 and is thus inhibited.

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