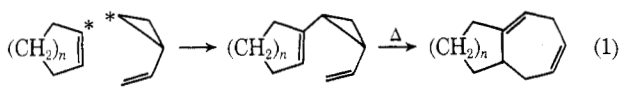
A Facile Route to Divinylcyclopropanes. An Efficient Method for the Annelative Formation of Functionalized Cycloheptanes

Summary: The reaction of *cis*- and *trans*-1-lithio-2-vinylcyclopropanes with 3-alkoxyenones provides an efficient, stereospecific route to various *cis*- and *trans*-1,2-divinylcyclopropanes and rearrangement of the latter compounds allows for the overall annelative formation of functionalized cycloheptanes; extension of this study to the preparation of cyclohept-4-enones is exemplified by the synthesis of karahanaenone.

Sir: The paucity of general methodology for the direct formation of functionalized seven-membered carbocycles and the occurrence of such ring systems in an increasing number of natural products[1] of biological importance has prompted our interest in developing methods which would provide for the efficient annelative formation of functionalized cycloheptanes. In connection with our synthetic objectives, an annelation strategy was sought which, from a topological viewpoint, would allow for the conjunction of a five-carbon synthon and an appropriately functionalized two-carbon unit. As outlined in eq 1, this objective could be realized through

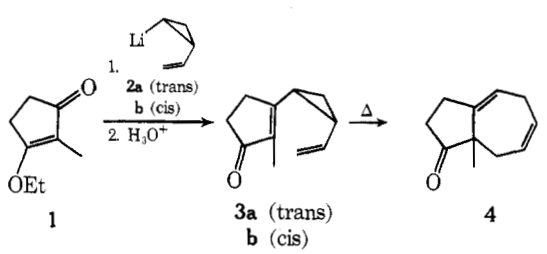


(1)

the attachment of a suitably activated vinylcyclopropane to a double bond or its latent equivalent to form a divinylcyclopropane subunit which upon thermal rearrangement[2] would be expected to afford the desired annelated product possessing strategically located functionality for subsequent synthetic utilization. The effectiveness of this sequence is contingent upon the development of a facile route to the divinylcyclopropane intermediate for which only limited and frequently circuitous methodology is available. This communication describes an efficient and operationally straightforward route to divinylcyclopropanes and applications of this method in synthesis.

Attention was initially focused on the reaction of 1-lithio-2-vinylcyclopropanes with 3-alkoxyenones (Scheme I) owing

Scheme I

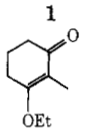
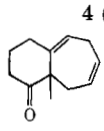
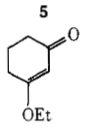
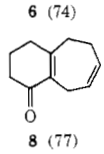
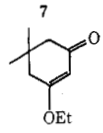
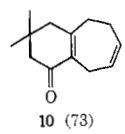
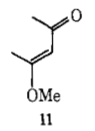
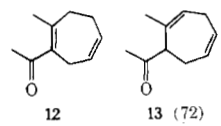


to the availability of the starting materials and the potential of the resulting functionality in subsequent synthetic operations. As such, *trans*-1-bromo-2-vinylcyclopropane[3] was converted to the lithiocyclopropane **2a** by reaction with *tert*-butyllithium (*t*-BuLi) in ether–pentane solvent at −78 °C. Addition of 3-ethoxy-2-methylcyclopent-2-enone (1) to this solution followed by hydrolysis of the reaction mixture with aqueous hydrochloric acid provided in high yield the *trans*-divinylcyclopropane product **3a**.[4,5] In a similar fashion, the reaction of reagent **2b**[3] with enone **1** afforded exclusively the *cis*-divinylcyclopropane product **3b**.[5-7] In accord with studies on the configurational stability of lithiocyclopropanes,[8] the above results indicate that the stereochemistry of the 1-bromo-2-vinylcyclopropanes is retained during the course of the metallation, addition, and hydrolysis reactions.

The viability of the second step of the annelation sequence became apparent when it was found that a pure sample of *cis*-divinylcyclopropane **3b** (ir 1695 cm^{-1}), which had been stored in a sealed vial for several days at ambient temperature, gradually became enriched in a second component (ir 1740 cm^{-1}). Moreover, attempted distillation of **3b** provided in excellent yield a single compound (ir 1740 cm^{-1}) which was subsequently established as the desired annelated product **4**.[5,9] Furthermore, the thermolysis of the *trans*-divinylcyclopropane **3a** [in solution (sealed tube) or neat] also provided dienone **4** in high yield. As anticipated from earlier studies on the divinylcyclopropane rearrangement[2] and in further support of the above stereochemical assignments of the divinylcyclopropanes, the cis compound **3b** rearranges with a half-life of 30 min at 80 °C (10% CCl_4 solution, sealed Pyrex tube) while the trans isomer **3a** has a half-life of 38 min at 160 °C (10% CCl_4 solution, sealed Pyrex tube).

A particularly attractive feature of the above method is that the entire annelation sequence can be performed in one synthetic operation, i.e., initial reaction (1,2 addition of the reagent), acidic workup (formation of the divinylcyclopropane), and distillation (rearrangement and purification). As shown in Table I, the annelation sequence is readily extended to various cyclic and acyclic 3-alkoxyenones. While substitution on the 3-alkoxyenone has no effect on the overall efficiency of the sequence, ketones **7**, **9** and **11** afford annelated products resulting from isomerization of the proximate β,γ-unsaturated product of the rearrangement under the conditions of the thermolysis.

Table I

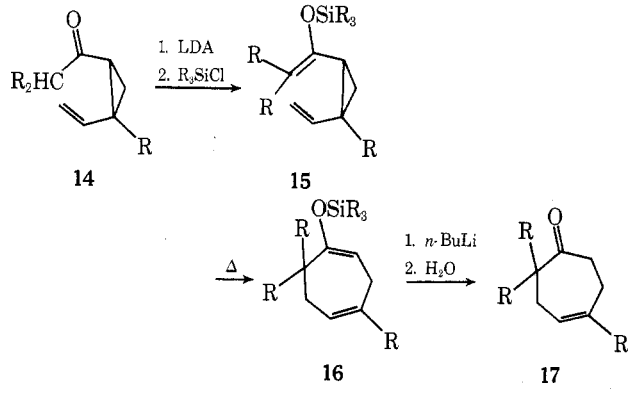
3-Alkoxyenone	Annelated product[a] (overall yield)[a]
1	**4** (72)
 **5**	 **6** (74)
 **7**	 **8** (77)
 **9**	 **10** (73)
 **11**	 **12** **13** (72)

[a] Yield of purified product based on 3-alkoxyenone.

A typical procedure for the above sequence is described below for the conversion of alkoxyenone **1** to ketone **4**. To a −78 °C ether (80 ml) solution of 1-bromo-2-vinylcyclopropane (40 mmol, 7:3 mixture of cis and trans) was added *t*-BuLi (48 mmol, 1.5 M in pentane) over 5 min. The resulting solution was stirred for 1.5 h at −78 °C and subsequently warmed to 0 °C. An ether (10 ml) solution of alkoxyenone **1** (20 mmol) was then added over a period of 2 min. The reaction mixture was stirred for 15 min at 0 °C and 15 min at ambient temperature and then carefully poured into a separatory funnel containing 2 N HCl (100 ml). Intermittent agitation of the above mixture (15 min) followed by standard workup provided in 91% yield (90% purity) the divinylcyclopropanes **3a** and **3b** (7:3 mixture of cis and trans), which were purified by silica gel chromatography (ether–hexane, 3:7).[7] Compounds **3a** and **3b** (2 M benzene solution) upon thermolysis (170–180 °C, 2 h) in a sealed Pyrex tube provided after purification ketone **4** (bp 54–59 °C, 0.15 mm) in 87% yield. Alternatively ketone **4** can be prepared by heating (250 °C, 5 min) the crude mixture of compounds **3a** and **3b** in a distillation apparatus followed directly by distillation of ketone **4**. In either case the method offers an exceptionally straightforward route to the annelated product with an overall yield of 72%.

The above strategy could be readily extended to other cycloheptane systems by varying the starting substrate (latent double bond equivalent). For example, aldehydes could be readily converted to acylvinylcyclopropanes **14** which could be used in the preparation of cyclohept-4-enones as outlined in Scheme II.

Scheme II



In order to test the efficacy of this route to cycloheptenones and examine variations in the lithio reagents, we have investigated this strategy in an approach to karahanaenone (**17**, R = Me).[10] Thus, a mixture of *cis*- and *trans*-1-lithio-2-methyl-2-vinylcyclopropane,[11] obtained from the metallation of the corresponding bromides, upon reaction with isobutyraldehyde and oxidation (pyridinium chlorochromate)[12] of the resulting alcohols provided a mixture of ketones **14** (R = Me, cis and trans). Treatment of this mixture with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by quenching with trimethylsilyl chloride afforded the siloxydivinylcyclopropanes **15** (R = Me, cis and trans). Thermolysis (165–175 °C, 1.5 M benzene solution) of this mixture followed by desilylation (*n*-BuLi, THF, 25 °C, 5 h) of the resulting diene **16** (R = Me) provided karahanaenone (**17**, R = Me) in an overall yield of 54% based on isobutyraldehyde.

Studies on the preparation of more highly functionalized reagents and the application of these reagents in synthesis are in progress.

Acknowledgments. The authors gratefully acknowledge the Research Corporation for financial support of this work. Exact mass analyses were performed by the NIH sponsored Biotechnology Research Resource for mass spectrometry at Massachusetts Institute of Technology.

References and Notes

(1) For listing of more than 100 examples of natural products with a seven-membered ring subunit, see T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Vol. II, Academic Press, New York, N.Y., 1972. For recent syntheses in one of the above areas, the pseudoguaianolides, see R. A. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976), and J. A. Marshall and R. H. Ellison, *ibid.*, **98**, 4312 (1976).
(2) For recent reports on the viability of such rearrangements, see J. P. Marino and T. Kaneko, *Tetrahedron Lett.*, 3975 (1973), and J. P. Marino and T. Kaneko, *J. Org. Chem.*, **39**, 3175 (1974). For the original report and studies on the mechanistic and synthetic aspects of the divinylcyclopropane rearrangement, see E. Vogel, *Angew. chem.*, **72**, 4 (1960); W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963); J. E. Baldwin and C. Ullenius, *J. Am. Chem. Soc.*, **96**, 1542 (1974); S. J. Rhoads and C. F. Brandenburg, *ibid.*, **93**, 5805 (1971); and S. J. Rhoads and J. M. Watson, *ibid.*, **93**, 5813 (1971).
(3) The pure *cis*- and *trans*-1-bromo-2-vinylcyclopropanes were obtained in preparative quantities by spinning-band distillation of the mixture of bromides prepared from butadiene. For the preparation of the bromides, see L. Skattebøl, *J. Org. Chem.*, **29**, 2951 (1964), and D. Seyferth, H. Yamazaki, and D. L. Alleston, *ibid.*, **28**, 703 (1963). For stereochemical assignments, see J. Landgrebe and L. Becker, *ibid.*, **33**, 1173 (1968).
(4) Compound **3a:** ir (neat) 1695 and 1635 cm^{-1}; NMR (CCl_4) δ 0.80–2.4 (complex m with br s at 1.71, 11 H) and 4.80–5.68 (m, 3 H).
(5) All new compounds reported were homogeneous by TLC or VPC and gave satisfactory ir and NMR spectra and exact mass or combustion analyses.
(6) Compound **3b:** ir (neat) 1695 and 1635 cm^{-1}; NMR (CCl_4) δ 0.80–2.60 (complex m with br s at 1.71, 11 H) and 4.80–5.50 (m, 3 H).
(7) Alternatively the divinylcyclopropanes may be isolated by distillation in which case the distillate is contaminated with varying amounts of the annelated product depending on the temperature used for the distillation. Pure samples of **3b** obtained by silica gel chromatography, upon standing at ambient temperature, slowly rearranged into compound **4**. In the other cases reported in Table I isolation of the intermediate *cis*-divinylcyclopropanes can only be accomplished by low temperature chromatography owing to significant rearrangement at room temperature.
(8) D. E. Applequist and A. H. Peterson, *J. Am. Chem. Soc.*, **83**, 862 (1961); H. M. Walborsky, F. J. Impastato, and A. E. Young, *ibid.*, **86**, 328 (1964); and M. J. S. Dewar and J. M. Harris, *ibid.*, **91**, 3652 (1969).
(9) Compound **4:** bp 54–59 °C (0.15 mm); ir (neat) 1740 cm^{-1}; NMR (CCl_4) δ 1.09 (s, 3 H), 2.05–3.10 (complex m, 8 H), and 5.30–5.77 (m, 3 H).
(10) Y. Naya and M. Kotake, *Tetrahedron Lett.*, 1645 (1968); E. Demole and P. Enggist, *Helv. Chim. Acta*, **54**, 456 (1971).
(11) The procedure in ref 3 provides a 54% yield (based on bromoform) of a mixture of bromides.
(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(13) Dreyfus Foundation Fellow, 1975–1976.

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Alkylation and Michael Additions of Glycine Ethyl Ester. Use in α-Amino Acid Synthesis and as Acyl Carbanion Equivalent

Summary: The benzylidene derivative of glycine ethyl ester can be used in mono- or sequential dialkylations thus leading to very simple syntheses of α-amino esters and acids; michael addition can also be effected readily, especially in protic solvents; the α-amino ester functionality can be transformed into a carbonyl (lithium aluminum hydride; periodate) and glycine ethyl ester is thus an acyl carbanion equivalent.

Sir: We would like to report that the readily available benzylidene derivatives of glycine esters can be alkylated in high yield under a variety of conditions. This obviously provides a particularly simple route to α-amino acids.[1]

It is especially noteworthy that the relatively high acidity of **1** permits formation of the anion and its alkylation not only with strong bases like lithium diisopropylamide, but with weaker bases such as potassium *tert*-butoxide. Also noteworthy is the fact that these alkylations can be performed not only with the *tert*-butyl ester, but are very satisfactory with the simple ethyl ester, in spite of the "extreme instability" claimed for this substance.[2] Because an α-amino ester is a masked carbonyl group, the anion of a benzylidene glycine ester is also an acyl carbanion equivalent.[3] The latent carbonyl function may be unmasked, inter alia, via the sequence lithium