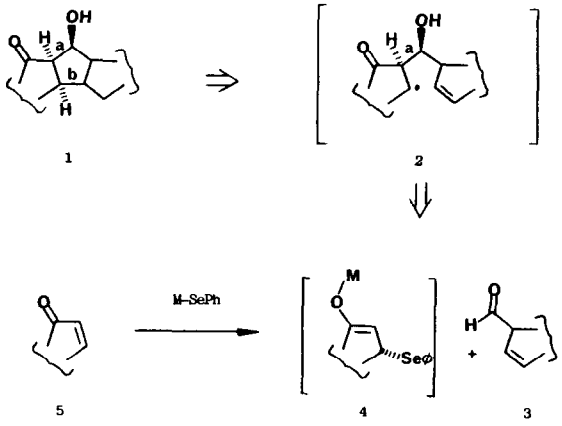
Tetrahedron Letters,Vol.26,No.52,pp 6431-6434,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHETIC APPLICATIONS OF THE TANDEM ALDOL CONDENSATION-RADICAL CYCLIZATION SEQUENCE. A NEW AND HIGHLY CONVERGENT METHOD FOR THE ANNULATION OF CARBOCYCLES

William R. Leonard and Tom Livinghouse*
Department of Chemistry
University of Minnesota
Minneapolis, MN 55455

Summary: The sequential treatment of α,β-unsaturated ketones with (phenylseleno)alanes or titanates followed by representative β,γ-unsaturated aldehydes has been shown to furnish β-(phenylseleno)ketols in high yield. The reductive cyclization of these species in the presence of tri-n-butyltin hydride affords the corresponding condensed carbocycles with high efficiency.

New carboannulation procedures which are convergent in nature and proceed under mild reaction conditions will assume prominent future roles in organic synthesis. Our interest in the development of an efficient synthetic route to the polyquinane sesquiterpenes has recently led us to develop a practical method for effecting annulations of this type. Our fundamental approach to this objective entails the stepwise fusion of a β,γ-unsaturated aldehyde (e.g., 3) to an enone (e.g., 5) via an aldol condensation-radical cyclization sequence (Scheme I).

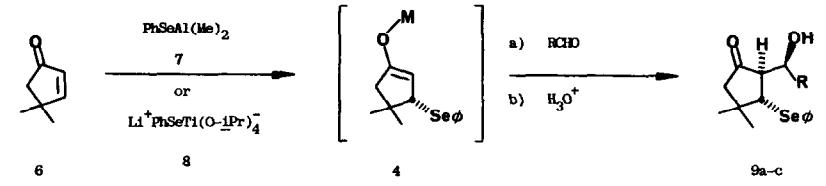


1 2 5 4 3

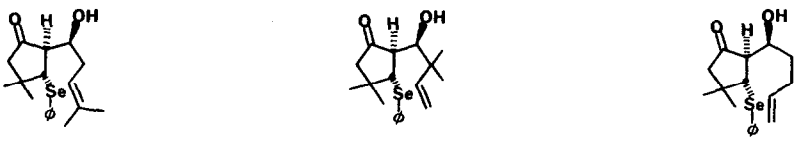
SCHEME I

The β-(phenylseleno)ketols 9a-c utilized in this study were efficiently prepared by the treatment of 4,4-dimethylcyclopent-2-en-1-one (6) with (phenylseleno)dimethylalane (7)[1a,b] or lithium (phenylseleno)tetraisopropoxytitanate (8)[2,3] followed by the appropriate β,γ- or γ,δ-unsaturated aldehyde. Accordingly, exposure of 6 to 7 (THF, -78 °C, 75 min) followed by the addition of 4-methylpent-3-en-1-al[5] (-78 °C, 15 min) afforded the trans, erythro-β-(phenylseleno)ketol 9a as the predominant product (erythro/threo: > 20/1) in 72% isolated yield.[6] The β-(phenylseleno)ketols 9b and c were prepared in an analogous manner via the condensation of 6 with 2,2-dimethylbut-3-en-1-al[7] ($PhSeAlMe_2$, THF -78 °C) or pent-4-en-1-al[7]

($Li^+PhSeTi(i\text{-}PrO)_4^-$, Et_2O, -30 °C→0 °C) in 63% and 71% isolated yield respectively. In all instances, products possessing a trans relationship between the β-(phenylseleno) moiety and the pendant aldol linkage were formed as the exclusive isomers. Moreover, a noteworthy preference for the formation of aldol isomers with the erythro configuration (erythro/threo: 8/1-20/1) was observed in all cases when the organometallics 7 and 8 were utilized.[8]

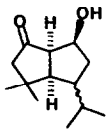


6 8 4 9a-c

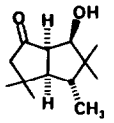


9a 9b 9c

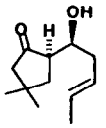
We next focused our efforts on the reductive cyclization of the substrates 9a-c. To our delight, addition of a solution of tri-n-butylin hydride (1.5 equiv.) and a catalytic quantity of AIBN in $PhCH_3$ via mechanical syringe over 16 h to **9a** in $PhCH_3$ at reflux furnished the bicyclic ketols **10 a,b** (**10a/10b**: 1/1) in 95% chromatographed yield.[9,10] The reductive cyclization of **9b** (n-Bu_3SnH, 1.5 equiv., $PhCH_3$, reflux) proceeded stereospecifically to afford the bicyclic ketol **11** (mp 86-89 °C) in 80% purified yield.[11] By way of contrast, the attempted free radical cyclization of **9c** under a variety of reaction conditions gave only the reductive rearrangement product **12**. Presumably, **12** arises by way of a "favored" 6-centered intramolecular hydrogen atom transfer[12] followed by reductive termination (Scheme II).



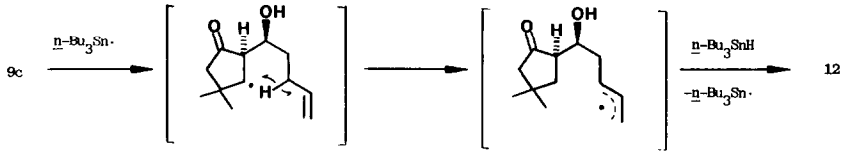
10a,b



11



12



SCHEME II

The synthetic viability of the tandem aldol condensation-radical cyclization sequence for the elaboration of functionalized bicyclo[3.3.0]octanes has been established. The utilization of this experimental protocol for the construction of polyquinane skeletal systems will be reported in due course.

Acknowledgement: Support for this research by a grant from the National Institute of Health (GM 32000) is greatfully acknowledged. This communication is dedicated to the memory of Professor Robert V. Stevens.

Literature Cited and Footnotes:

1. (a) (Phenylseleno)-dimethylalane (7) was conveniently prepared by the treatment of trimethylaluminum with 1 equiv. of selenophenol in $PhCH_3$ (-78 °C→0 °C). This preparation is analogous to that utilized for the synthesis of (phenylthio)dimethylalane:1(b) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H., Bull. Chem. Soc. Jpn., 1981, 54, 274.
2. Lithium (phenylseleno)tetraisopropoxytitanate (8) was conveniently prepared in situ via the deprotonation of selenophenol in ether with n-BuLi followed by the addition of one equiv. of titanium (IV) isopropoxide.

3. In variance with our expectations, 9-(phenylseleno)-9-borabicyclononane[4] possessed limited utility for the synthesis of β-(phenylseleno)ketols (e.g., 9a-c) from the corresponding enones and unsaturated aldehydes. This discrepancy is attributable to the robust nature of boron aldolates toward hydrolytic decomplexation.
4. Leonard, W. R.; Livinghouse, T., J. Org. Chem., 1985, 50, 730.
5. Julia, M.; Le Thuillier, G., Bull. Soc. Chim. Fr., 1966, 717.
6. The exceedingly mild nature of this "neutral" aldol condensation is reflected by the absence of double bond isomerization in the sensitive β,γ-unsaturated aldehyde 4-methylpent-3-en-1-al.
7. 2,2-Dimethylbut-3-en-1-al and pent-4-en-1-al were conveniently prepared by the oxidation of the corresponding alcohols using pyridinium chlorochromate or $CrO_3 \cdot 2C_5H_5N$, respectively in CH_2Cl_2.
8. The high erythro selectivity in these aldol condensations is presumed to be a kinetic phenomenon.
9. All yields correspond to purified products. All new compounds have been fully characterized by 300 MHz NMR and IR spectroscopy and possess satisfactory elemental (C, H) analyses or exact mass.
10. The aldols 10a,b were demonstrated to be isomeric at the isopropyl bearing γ-carbon on the basis of chemical and spectroscopic evidence. Specifically, sequental mesylation-elimination of each isomer provided the corresponding enones which were also isomeric. Moreover, NOED studies revealed a cis relationship between the aldol, α-, and β- methines in both isomers.
11. Support for the stereochemical assignment of 11 was provided by NOED spectroscopy. A definitive assignment awaits single crystal x-ray structure determination.
12. Stork, G. in "Selectivity - a Goal for Synthetic Efficiency", pp. 281-298, Bartmann, W.; Trost, B. M. Eds., Verlag Chemie, 1984, Weinham.

(Received in USA 3 October 1985)