Pergamon

Tetrahedron, Vol. 52, No. 22, pp. 7737-7744, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00341-9

Synthesis of Linearly Fused Tricyclic Compounds *via* Thermal Oxy-Cope Rearrangement

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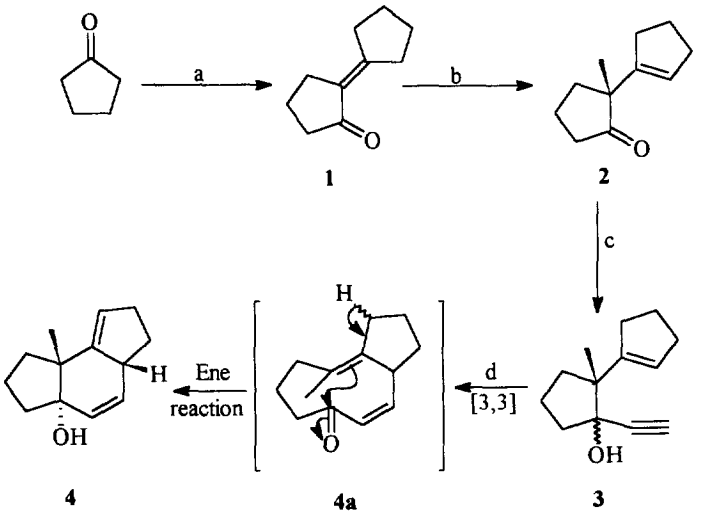
Abstract : Linearly fused tricyclic [5.6.5] and [6.6.6] compounds **4, 6, 10** and **12** were prepared from ethynyl and allenyl derivatives of self condensed cycloalkanones **3, 5, 9** and **11** by thermal oxy-Cope rearrangement is described. Copyright © 1996 Elsevier Science Ltd

New strategies for the synthesis of linearly fused tricyclic systems have gained considerable prominence in recent years owing to the existence of these frameworks in many naturally occurring compounds[1]. The usefulness of oxy-Cope rearrangement towards the elaboration of complex ring systems present in a number of naturally occurring molecules has attracted the attention of synthetic organic chemists[2,3]. In continuation of our current interest in the synthesis of tricyclic systems *via* thermal oxy-Cope[4] rearrangement, the synthesis of ethynyl and allenyl derivatives of self condensed cycloalkanones **3,**



1 **2** **4** **4a** **3**

Reagents and conditions:

a) NaOH, 30% EtOH, 1h, RT, 60%
b) *t*-BuO$^-$K$^+$/ *t*-BuOH, CH_3I, RT, 6h,80%
c) 3 equi. LiC≡CH / THF, -78 °C , 2h, 85%
d) *o*-DCB, N_2 , reflux,12h, 55%

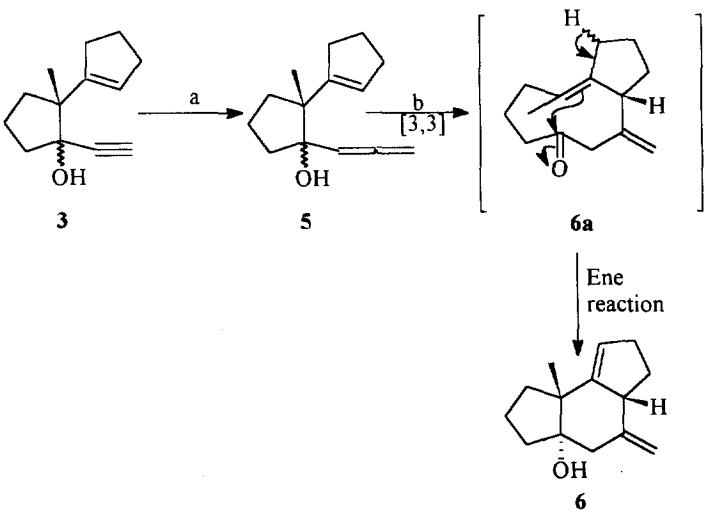
Scheme 1

5, 9 and **11** was undertaken. A key step in the synthesis of tricyclic systems reported herein is the thermal oxy-Cope rearrangement which leads to the ring -enlarged intermediates which subsequently cyclise *via* a second chemical event namely transannular ene type reaction. The later reaction not only depends upon the interatomic distances[4a] but also the proximity of the allylic hydrogen[5] to the carbonyl oxygen. It is notable that the oxy-Cope systems reported herein contain an allenic and acetylenic group as one of the participating π systems.

The synthesis and rearrangement of self condensed cyclopentanone ethynyl derivative **3** is detailed in scheme 1.

The self condensed cyclopentanone derivative **1** was prepared according to the literature procedure[6]. Compound **1** was methylated by treatment with *t*-BuO$^-$K$^+$ / *t*-BuOH, MeI, 6h under N_2 atmosphere to afford **2** in 80% yield. Addition of lithium acetylide (3 equi.) to **2** (2-methyl-2-(cyclopent-1'-yl)-cyclopentanone) in THF, at -78°C gave the ethynyl carbinol **3** in 85% yield.. Rearrangement of **3** in refluxing ortho dichlorobenzene (*o*-DCB) for 12h in an inert atmosphere and then removal of *o*-DCB under reduced pressure (< 0.5 torr) followed by column chromatography gave the tricyclic compound **4** in 55% yield. Compound **4** shows IR characteristic bands at 3500 cm^{-1} for OH and 1620 cm^{-1} for C=C. In ^{1}H NMR (90 MHz) signals at δ 5.4 (vinylic hydrogen) and δ 1.15 (angular methyl) were observed while ^{13}C NMR shows vinyl carbons at δ 145.35 (s), 121.61 (d), OH bearing carbon at δ 73.65 methyl bearing quarternary carbon at δ 43.32 (s) and methine carbon at δ 32.01 (d). Stereochemistry for compound **4** was assigned based on NOE studies[4a]. It is rationalised that the compound **4** is formed *via* the intermediate **4a** which undergoes a facile transannular ene type reaction.

The synthesis of allene[8] **5** and its rearrangement is detailed in scheme 2.



3 **5** **6a** **6**

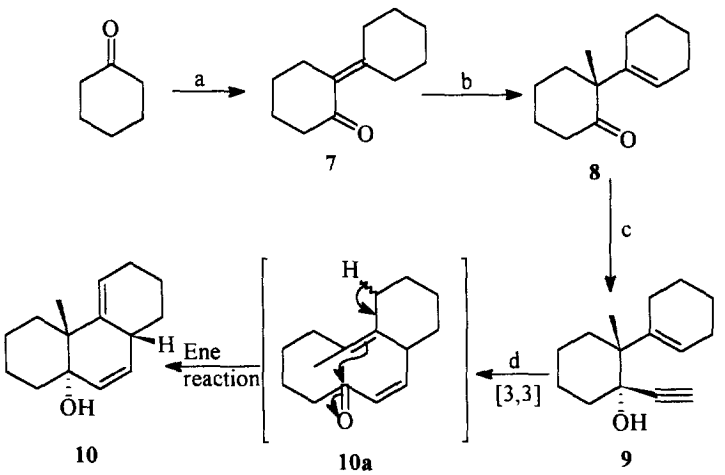
Reagents and conditions:

a) *i*-Pr$_2$NH, $(CH_2O)_n$, THF, CuBr, reflux, 6h, 60%, N_2 b) *o*-DCB, N_2, reflux, 12h, 50%

Scheme 2

Refluxing ethynyl carbinol **3** with diisopropylamine, paraformaldehyde and Cu(I)Br in THF[8] for 6h under nitrogen atmosphere afforded the allene **5** in 60% yield after chromatographic purification of silicagel column. The allene **5** shows IR characteristic bands at 3520 cm^{-1} (OH), 1955 cm^{-1} (allene moiety), and 1615 cm^{-1} (C=C). In the ^1H NMR signals at δ 4.8 and 5.4 a doublet and a multiplet were observed for the allene protons. In the ^{13}C NMR a singlet was observed at δ 210 ppm (C=C=C) for the allene central carbon. Rearrangement of allene **5**[7] as described for compound **3** gave the tricyclic compound **6** in 50% yield, which shows IR characteristic bands at 3510 cm^{-1} for OH, 2100 cm^{-1} for exocyclic double bond and 1610 cm^{-1} for double bond. In ^1H NMR signals at δ 4.8 (multiplet) for exocyclic double bond protons, and at δ 1-1.8, (multiplet) for methylene and OH protons, δ 0.9, (singlet) for angular methyl were observed.

Rearrangement study was extended to the self condensed cyclohexanone ethynyl derivative **9** which is outlined in scheme 3.



Reagents and conditions:

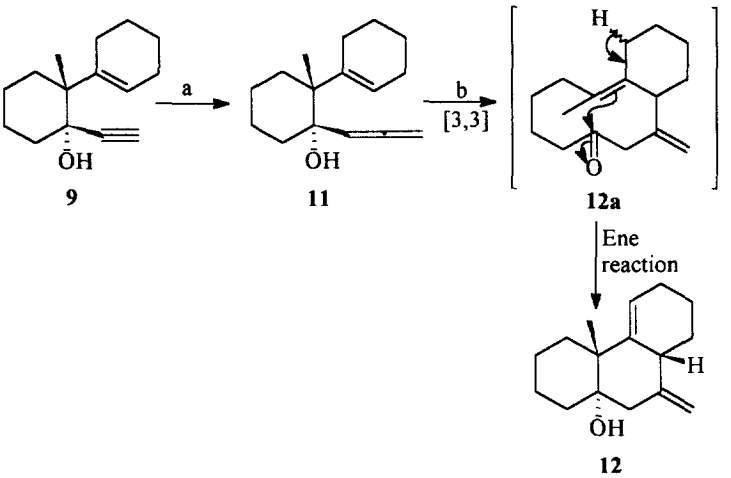
a) (i) dry HCl, 12h, (ii) NaOMe/ MeOH, 20°C b) *t*-BuO^-K^+/ *t*-BuOH, CH_3I, RT, 6h, 85%

c) 3 equi LiC≡CH / THF, -78°C, 2h, 90% d) *o*-DCB, N_2 , reflux, 12h, 54%

Scheme 3

Self condensation of cyclohexanone[9] followed by methylation as described for compound **1**, gave product **8** in 85% yield. Addition of lithium acetylide (3 equi.) to **8** in THF at -78 °C gave the known ethynyl carbinol[10] **9** in almost quantitative yield as a single diastereomer. Rearrangement of ethynyl carbinol **9** in refluxing *o*-DCB as described earlier gave compound **10** probably *via* the intermediate **10a**[7] in 54% yield.

The rearrangement study was also extended to self condensed cyclohexanone allenyl derivative **11** (scheme 4).



Reagents and conditions :

a) *i*-Pr_2NH, $(CH_2O)_n$, THF, CuBr, reflux, 6h, 65%, N_2 b) *o*-DCB, N_2 , reflux ,12h, 55%

Scheme 4

Allene[8] **11** was prepared from ethynyl compound **10** as described for allene **5** in 65% yield. Rearrangement of allene **11** under the conditions described for compounds **3, 5** and **9** furnished **12** in 55% yield. The tricyclic compound thus obtained was purified by column chromatography (Silica gel).

The facile transannular ene type reaction can be easily rationalised based on conformational representation of the intermediate ring enlarged compounds **4a**, **6a**, **10a**, and **12a** (Fig. 1). The stereochemistry of A/B (*trans*) ring fusion in the compounds **4, 6, 10** and **12** was established by NOE studies. Irradiation of the angular methyl group protons did not cause any change in the intensity of the signal due to the hydroxyl proton in all these compounds. From the molecular models of the conformations **4a, 6a, 10a** and **12a**, it could be safely concluded that the hydrogen at the 4-position (B/C ring junction) should end up *cis* to the angular methyl group in the process of undergoing the transannular type ene reaction. The molecular models clearly showed the proximity of the carbonyl oxygen and the allylic hydrogen, which is obviously a necessary condition for the ene type reaction.

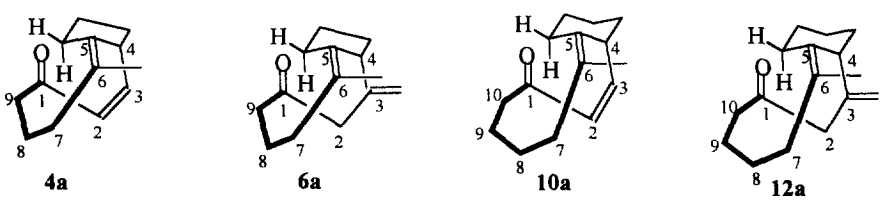


Fig. 1 Conformational representation of intermediates **4a, 6a, 10a** and **12a.**

All the compounds reported herein were fully characterised by spectral and analytical data. Further studies in this direction are in progress.

Experimental

General Consideration :

All melting points and boiling points are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 instrument. ^1H NMR(90 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on a Varian EM-390 and Jeol FX 90Q instruments respectively. Chemical shifts are reported in ppm(δ) with TMS as standard. Mass spectra were recorded on a JEOL JMS-DX 303 HF instrument. Elemental analysis was performed with a Perkin-Elmer 240B elemental analyser. Column chromatography was carried out with SiO_2 (ACME, 100-200 mesh). The organic extracts of crude products were dried over anhydrous $MgSO_4$. Solvents were reagent grade and were purified according to literature procedure[11].

General Procedure for Ethynylation [4] **:**

Lithium acetylide was prepared by the addition of *n*-BuLi [prepared from lithium (0.7g, 0.1g atom) and *n*-BuBr (6.85g, 0.05 mol) in dry ether at 0 - 10 °C] to a dry THF solution of acetylene at -78 °C. To this was added a solution of **2** (2 g, 0.012 mol) in dry THF (25 ml) dropwise during 15 minutes and the reaction mixture was maintained at -78 °C for 2h with constant stirring. Solid K_2CO_3 (10g) was added to the reaction mixture followed by water (20ml), and then extracted with ether (3 X 25 ml). The ether layer washed with water dried ($MgSO_4$) and concentrated at reduced pressure to furnish the ethynyl carbinol **3** which was purified by column chromatography (Silica gel). Similarly, compound **9** was prepared from **8** in 90 % yield.

***Data for compound* 3:**

Yield: 85% ; R_f = 0.3 (95:5, Hexane:EtOAc); IR (CCl_4) ν_{max} cm^{-1}: 3520(OH), 3300 (C≡C-H), 2100 (C≡C), 1620 (C=C). ^1H NMR (90 MHz, $CDCl_3$ / TMS) δ ppm : 1.22 (s, 3H, methyl), 1.3-2.3 (m,12H, methylenes), 2.7 (s,1H, ethynyl proton), 4.08 (s, 1H, OH), 5.6 (br s, 1H, vinylic hydrogen). Mass spectra *m/e* (M^+): 190 ; Elemental analysis : Calcd. for $C_{13}H_{18}O$ C= 82.06, H=9.53 %; found C= 82.00, H=9.50%.

***Data for compound* 9:**

Yield: 90% ; m.p 110-111°C (Hexane:CCl_4) ; R_f = 0.6 (95:5, Hexane:EtOAc) ; IR (CCl_4) ν_{max} cm^{-1}: 3500 (OH), 3300 (C≡C-H), 2100(C≡C), 1610 (C=C). ^1H NMR (90 MHz, $CDCl_3$ / TMS) δ ppm : 1.0 (s, 3H, methyl), 1.3-2.3 (m,17H, methylenes and OH), 2.7 (s,1H, ethynyl proton), 5.6 (br s, 1H, vinylic hydrogen). Mass spectra *m/e* (M^+):190; Elemental analysis : Calcd. for $C_{15}H_{22}O$ C= 82.56, H=10.37%; found C= 82.40, H=10.30%.

General Procedure for Allene Formation [8] **:**

A mixture containing ethynyl carbinol **3**(1mmol), freshly prepared Cu(I)Br (0.5 mmol) diisopropylamine (1.6 mmol) and paraformaldehyde (1.5 mmol) in THF was refluxed for 12h under N_2 atmosphere. After cooling, the inorganic material was filtered, diluted with ether, shaken with saturated brine solution and organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel column using hexane-ethyl acetate (9.5:0.5) as the eluent, to furnish compound **4** as a viscous liquid in 55% yield. Similarly, compound **11** was obtained as a viscous liquid from compound **10** in 54% yield.

***Data for compound* 5:**

Yield: 60% ; R_f = 0.4 (95:5, Hexane:EtOAc) ; IR (CCl_4) ν_{max} cm^{-1}: 3520 (OH), 1955 (C=C=C), 1615 (C=C). ^1H NMR (90 MHz,$CDCl_3$ / TMS) δ ppm : 1.0 (s, 3H, angular methyl), 1.5-2.5 (m,12H,

methylenes), 3.0 (br s,1H, OH), 4.8 (d, 1H, H-C=C=C), 5.4 (m, 2H, C=C=CH_2), 5.6(s, 1H, vinylic hydrogen). Mass spectra *m/e* (M^+):204; Elemental analysis : Calcd. for $C_{14}H_{20}O$ C= 82.30, H=9.87 %; found C= 82.25, H=9.77%.

***Data for compound* 11:**

Yield: 65% ; R_f = 0.4 (95:5, Hexane:EtOAc) ; IR (CCl_4) ν_{max} cm^{-1}: 3500 (OH), 1950 (C=C=C), 1610 (C=C). ^1H NMR (90 MHz, $CDCl_3$ / TMS) δ ppm : 1.2 (s, 3H, angular methyl), 1.4-2.4 (m,16H, methylenes), 3.0 (br s,1H, OH), 4.9 (d, 1H, H-C=C=C), 5.3 (m, 2H, C=C=CH_2), 5.9(s, 1H, vinylic hydrogen). Mass spectra *m/e* (M^+): 231; Elemental analysis : Calcd. for $C_{16}H_{24}O$ C= 82.75, H=10.34%; found C= 82.64, H= 10.19%.

General Procedure for Thermal oxy-Cope Rearrangement:

A solution of ethynyl or allenyl carbinol (5 mmol) in *o*-DCB (20 ml) was refluxed under nitrogen atmosphere for 12h. The solution was cooled, and the solvent was removed under vacuum (0.5 torr), and the residue was chromatographed over silica gel [hexane - ethylacetate(10:1)] to give the pure rearranged compounds.

***Data for compound* 4:**

Yield: 55% ; R_f = 0.6(90:10, Hexane:EtOAc) ; IR (CCl_4) ν_{max} cm^{-1}: 3500 (OH), 1620 (double bond). ^1H NMR (90 MHz, $CDCl_3$ / TMS) δ ppm : 1.1 (s, 3H, angular methyl), 1.5-2.5 (m, 12H, methylenes and OH), 4.8 (m, 1H, vinylic hydrogen), 5.4(AB q , 2H, olefinic protons) ; ^{13}C NMR (22.5 MHz, $CDCl_3$ / TMS) δ ppm : 145.3, 130.6, 126.3, 121.6, 73.6, 43.1, 31.6, 30.7, 30.1, 22.7, 22.2, 21.8, 21.3 ; Mass spectra *m/e* (M^+): 190 ; Elemental analysis : Calcd. for $C_{13}H_{18}O$ C= 82.10, H=9.47 %; found C= 82.15, H= 9.40%.

***Data for compound* 6:**

Yield: 50%; R_f = 0.5(90:10, Hexane:EtOAc) ; IR (CCl_4) ν_{max} cm^{-1}: 3510 (OH), 2100 (exocyclic double bond),1620 (double bond). ^1H NMR (90 MHz, $CDCl_3$ / TMS) δ ppm : 1.1 (s, 3H, angular methyl), 1.5-2.5 (m,14H, methylenes and OH), 5.4(s, 1H, vinylic hydrogen), 4.9(m ,2H, exocyclic protons); ^{13}C NMR (22.5 MHz, $CDCl_3$ / TMS) δ ppm : 145.5, 139.9, 121.2, 117.7, 74.1, 42.3, 35.1, 31.7, 31.3, 30.6, 30.2, 21.5, 21.0, 20.8 ; Mass spectra *m/e* (M^+): 205 ; Elemental analysis : Calcd. for $C_{14}H_{20}O$ C= 82.35, H=9.80%; found C= 82.30, H= 9.68 %.

***Data for compound* 10 :**

Yield: 54%; R_f = 0.5(90:10, Hexane:EtOAc) ; IR (CCl_4) ν_{max} cm^{-1}: 3500 (OH), 1610 and 1620 (double bonds). ^1H NMR (90 MHz, $CDCl_3$ / TMS) δ ppm : 0.8(s, 3H, angular methyl), 1.2-2.8 (m,15H, methylenes and OH), 5.3(s, 1H, vinylic hydrogen), 5.8 (d,1H, olefinic hydrogen) 6.2 (d,1H, olefinic hydrogen); ^{13}C NMR (22.5 MHz, $CDCl_3$ / TMS) δ ppm : 146.3, 143.1, 122.6, 121.4, 73.6, 43.3, 33.1, 32.0, 31.6, 30.8, 30.1, 22.1, 21.7, 21.2, 20.6 ; Mass spectra *m/e* (M^+): 218; Elemental analysis : Calcd. for $C_{15}H_{22}O$ C= 82.52, H=10.37%; found C= 82.45, H= 10.27 %.

***Data for compound* 12 :**

Yield: 55%; R_f = 0.5(90:10, Hexane:EtOAc); IR (CCl_4) ν_{max} cm^{-1}: 3500 (OH), 1950 (exocyclic double bond),1620 (double bond). ^1H NMR (90 MHz, $CDCl_3$ / TMS) δ ppm : 1.0 (s, 3H, angular methyl),

1.5-2.5 (m, 16H, methylenes), 2.9 (br s, 1H,OH), 4.8 (m ,2H, exocyclic protons), 5.5 (s, 1H, vinylic hydrogen); ^{13}C NMR (22.5 MHz, $CDCl_3$ / TMS) δ ppm : 146.1, 140.3, 123.2, 118.1, 73.6, 43.2, 34.0, 33.1, 32.1, 31.6, 30.7, 30.2, 21.9, 21.1, 21.0, 20.6 ; Mass spectra *m/e* (M^+): 232; Elemental analysis : Calcd. for $C_{16}H_{24}O$ C= 82.75, H=10.34%; found C= 82.69, H= 10.48%.

Acknowledgement

PS thanks CSIR (New Delhi) for junior and senior research fellowship. He also thanks Dr. S. Janardhanam, Dr. B. Devan, University of California, Davis, USA, Dr. A. Balakumar, Parry India Ltd, Madras and Dr. G. Vijay Nair, Deputy Director, Regional Research Laboratory (CSIR), Trivandrum for useful discussion. Special Assistance (SAP) from UGC (New Delhi) to this department is gratefully acknowledged. The authors thank the referee for the constructive suggestions.

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7. (a) Evaluation by means of MMX calculation using a PC model for intermediates **4a, 6a, 10a,** and **12a** gave transannular gap 3.52, 3.10, 3.86, 3.36 A between C_1 _C_6 atoms respectively for potential cyclization.
(b) Constructing molecular models for intermediates **4a, 6a, 10a,** and **12a** showed that one of the allylic hydrogen in the ring is in close proximity to the carbonyl oxygen, thereby making transannular ene reaction a feasible mode of reaction for the ring enlarged intermediate.
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(*Received in UK* 12 *February* 1996; *revised* 1 *April* 1996; *accepted* 2 *April* 1996)