



A short synthesis of 1,5-cyclooctadiene macrocycles

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ABSTRACT

5- Cyclooctadiene derivatives were synthesized by domino intermolecular alkylation and cycloalkylation of 2 -(3,4-dihydro-1-naphthenyl) ethanols, which were obtained from tetralones, by Reformatsky reaction followed by LAH reduction. These 8-membered macrocycles have the carbocyclic frame work of several terpenoids.

Keywords: 8-Membered macrocycles, domino intermolecular alkylation and cycloalkylation, 1,5cyclooctadiene, Reformatsky reaction.

INTRODUCTION

The term macrocycles[1] broadly refers to medium (8 to 11 atoms) and large (12 or more atoms) ring compounds. Macrocyclic chemistry is undergoing a period of intensive growth. The past decade has seen development of new methods for the synthesis of macrocycles, elucidation of their physical and chemical properties and ever increasing study of the more complex, naturally occurring compounds possessing medium and large cycles as structural elements.

Although eight membered rings are not as abundant as some of the smaller ring sizes, they occur widely in nature, particularly in higher plants and marine organisms[2]. There are over one hundred known terpenoid natural products[3-12]containing eight membered carbocyclic ring in their structure. Compounds of this type have been isolated from a variety of sources including terrestrial plants, marine organism and fungi. The eight membered carbocyclic ring compounds exhibit biological activities such as anticancer[13], antibiotic[14], cardiotoxic[15], antihypertensive[16]and plant growth regulator.[17]

The conformational properties of molecules containing eight membered rings have been studied extensively. Spectroscopic methods (NMR, IR and X-ray), crystallography and molecular mechanism calculations [18]have revealed that there are three major conformational families: the boat-chair, crown and boat- boat. The most stable conformation is usually the boat-chair, which minimizes transannular interaction and has a low torsional strength.We now wish to report a new synthesis of the title compounds from 2 -(3,4-dihydro-1-naphthenyl) ethanols.

EXPERIMENTAL SECTION

Reagents were of LR grade and were used without further purification. Column chromatography was carried out using silica gel (S. D. Fine Chemicals, India) 60-120 mesh. Boiling point of Petroleum ether used was in the range of 60-80 °C. The melting points (uncorrected) were determined on a Gallenkamp melting apparatus. The IR spectra (wave numbers in cm^{-1}) were recorded on a Shimadzu FTIR-4200 spectrometer either as oil film or KBr discs. UV spectra were recorded on a Shimadzu UV-Visible spectrophotometer UV-2100. $^1\text{H-NMR}$ spectra were recorded on Bruker 300 (300 MHz) instrument in CDCl_3 with tetramethylsilane as internal standard. $^{13}\text{C-NMR}$ spectra were recorded on Bruker AVANCE (75MHZ) spectrometer. Mass spectra were recorded on API-3000MD-series (US).

Chemical shifts are given in ppm and coupling constants (*J*) in Hz. Elemental analyses were carried out on a Carlo ErbaEA-1108 elemental analyser.

2-(3,4-dihydro-1-naphthalenyl) ethanol.[19] (**XI**) yellow oil(61.2%)

2-(3,4-dihydro-7-methyl-1-naphthalenyl) ethanol (**XII**)

yellow oil(65%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3350-3450(O-H str.), 3100(Ar- C-H str.), 2860-2980 (C-H str.), 1600, 1460, (Ar- C=C), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 1.9-3.00 (m, 10H, H-3, H-4' and 1 - OH); 3.74 (t, 2H, O-CH₂); 5.75 (t, 1H, C=C-H); 6.66-7.25 (m, 3H, Ar-H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 24.7(Ar-Me), 28.8(C-4), 31.3(C-3), 40.6(C-9), 60.5(O-CH₂), 115.7(C=C-H), 126.6(C-8), 127.6(Ar-4), 128.2(Ar-4''), 134.8(C-8''), 135.0 (C-1), 135.5(Ar-6), 144.2(C-1), UV (CHCl_3) λ_{\max}/nm (log ϵ): 266(3.8044), Analysis calc. for C₁₃H₁₆O: C, 82.94; H, 8.57. Found: C, 82.86; H, 8.52.

2-(3,4-dihydro-6,7-dimethyl-1-naphthalenyl) ethanol (**XIII**)

yellow oil(63.8%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3350-3450(O-H str.), 3100 (Ar-C-H str.), 2860-2950 (ali C-H str.), 1450, 1500 and 1600 (Ar- C=C str.), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 1.9-3.00 (m, 13H, H-3, H-4, H-1', H-2', 1-OH); 3.75 (t, 2H, -OCH₂); 5.73 (t, 1H, -C=C-H); 6.8 (s, 1H, Ar-H₅); 7.1 (s, 1H, Ar-H₈), $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 18.1 (Ar-CH₃), 18.2 (Ar-CH₃), 29.1(C-3), 31.3(C-3), 40.6(C-9), 60.5(C -OH), 115.7(C-2), 126.5(C-8), 129.4(C-5), 134.0(C-7), 136.0(C-6), 135.2(C-4'), 131.8(C-1'), 144.2(C-1), UV (CHCl_3) λ_{\max}/nm (log ϵ): 266.8(3.6684), Analysis calc. for C₁₄H₁₈O: C, 82.94; H, 8.57. Found: C, 82.86; H, 8.52.

2-(5-chloro-3,4-dihydro-1-naphthalenyl) ethanol(**XIV**)

yellow oil(60.9%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3350-3450 (O-H str.); 3010-3100 (Ar- C-H str.); 2860, 2950 (C-H str.); 1460, 1580 and 1605 (Ar- C=C str.), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 2.3 (m, 7H, H-3, H-4, H-1' and 1 - OH); 3.66-3.73 (t, 2H, O-CH₂); 5.76-5.83 (t, 1H, C=C-H); 6.66-7.5 (s, 3H, Ar-H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 14.1(Me), 19.4(C-4), 30.2(C-3), 42.9(C-9), 61.4(-OCH₂), 135.7(C-1), 116.5(C-2), 124.4(C-8), 127.3(C-7), 128.0(C-6), 133.0(C-5), 136.3(C-1'), 138.3(C-4'), 168.2(-CO). MS(*m/z*(rel.%)): 210(M⁺+2, 22.2%); 208 (64.4%), 190 (14.4%); 179 (11.1%); 177 (46.6%); 175 (53.3%); 166 (13.3%); 165 (40%); 164 (55.5%); 163 (82.2%); 162 (64.4%); 156 (13.3%); 155 (100%); 154 (15.5%); 153 (18.8%); 149 (15.5%); 143 (26.6%); 141 (82.2%); 139 (26.6%); 129 (33.3%); 128 (73.3%); 127 (57.7%); 126(13.3%); 115 (62.2%). UV (CHCl_3): Analysis calc. for C₁₂H₁₃ClO: C, 69.07; H, 6.28, Cl, 16.99. Found: C, 69.15; H, 6.31, Cl, 16.92.

2-[3,4-dihydro-7-(2-propyl)-1-naphthalenyl] ethanol(**XV**)

yellow oil(59.2%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$:3370-3450 (O-H str.). 3010-3100 (Ar- C-H str.); 2860-2950 (C-H str.); 1460, 1510 and 1600 (Ar- C=C str.), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 1.23(d, 6H, CH(CH₃)₂), 2-3 (m, 8H, 7 C-Hali. and 1 - OH), 3.66 (t, 2H, O-CH₂), 5.73 (t, 1H, OC-H), 6.66-7.4 (m, 3H, Ar-H), $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 23.4 (2Me), 28.8(C-4), 31.3(C-3), 36.7(-CH<), 60.5(C-OH), 115.7(CH=C), 123.7(C-8), 125.3(C-6), 127.4(C-5), 134.8(C-1'), 135.5(C-4'), 145(C-7), 144.2(C-1), 40.6(C-9), UV (CHCl_3) λ_{\max}/nm (log ϵ):262.7 (3.8423). Analysis calc. for C₁₅H₂₀O: C, 83.29; H, 9.32. Found: C, 83.34; H, 9.29.

RESULTS AND DISCUSSION

Cycloalkenylethanols(**XI**,**XII**,**XIII**,**XIV**,**XV**) were synthesised from tetralones(**I-V**) according to the reported procedure[20-22](**Scheme**).

Toward this end five tetralones (**I**,**II**,**III**,**IV**,**V**) were prepared and these were subjected to Reformatsky reaction to afford the corresponding ethyl 3,4-dihydro-1-naphthenyl acetates(**VI**,**VII**,**VIII**,**IX**,**X**). These esters were subjected to LAH reduction to yield the corresponding 2-(3,4-dihydro-1-naphthenyl) ethanol(**XI**,**XII**,**XIII**,**XIV**,**XV**).

To begin with 2-(3,4-dihydro-1-naphthenyl) ethanol (**XI**) was reacted in PPA by heating on steam bath for 4 hours. The reaction on work up gave colorless oil of (**XVI**)

A perusal of the spectral data reveals that the oily compound obtained from the reaction showed absence of -OH group in its IR spectrum and -OH and alkenic proton in $^1\text{H-NMR}$ indicating the participation of these centers during the above reaction.

The $^1\text{H-NMR}$ spectrum showed seven signals appearing at δ =2.00, 2.29, 2.59, 7.03, 7.07, 7.09 and 7.25 indicating the presence of two types of allylic and four types of aromatic protons. The signal appearing at δ = 2.59 accounts for the remaining 4H benzylic proton.

^{13}C spectrum also confirmed the presence of a tetra substituted alkene (124.00, 127.30).

The mass spectrum showed M^+ at $m/z=312$ suggesting the formation of 5, 6, 7, 8, 13, 14, 15, 16-octahydrocycloocta[1,2-*a*:5,6-*a'*]dinaphthalenes(IX).

Similarly other ethanols gave the corresponding 1,5-cyclooctadiene derivatives(XVII, XVIII, XIX, XX). Thus during this reaction, ethanols underwent domino intermolecular alkylation and cycloalkylation.

General procedure for domino intermolecular alkylation and cycloalkylation:

A mixture of 2-(1-naphthalenyl)ethanols(XI-XV)(2.16 gm) and PPA (10 g) was heated on steam bath for 4 hours. The reaction mixture was poured onto the ice and extracted with ethyl acetate (3 x 25 ml). The combined ethyl acetate extract was washed with 10% sodium carbonate, water (2 x 25 ml) and then dried (anhydrous sodium sulphate). Recovery of solvent afforded a dark oil, which was purified by column chromatography using silica gel adsorbent. Elution with petroleum ether (600 ml) followed by recovery of solvent afforded a colourless oil 5,6,7,8,13,14,15,16-octahydrocycloocta [1,2- *a*:5,6-*a'*]dinaphthalenes(XVI-XX).

5,6,7,8,13,14,15,16-octahydrocycloocta [1,2- *a*:5,6-*a'*]dinaphthalene (XVI)

colourless oil (66%)

IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3015-3057 (v Ar-C-H), 2925 (v C-H), 2859 (v C-H), 1622 (v C=C), 1600 (Ar-C-H), 1449, 1488 (v C-H), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 2.00 (s, 8H; H-7, H-8, H-15 H-16), 2.29 (t, 4H; H-6, H-14), 2.59 (t, 4H; H-5, H-13), 7.03-7.25 (m, 2H: Ar-H-2, Ar-H-10), 7.07 (m, 2H: Ar-H-4, Ar-H-12), 7.09 (m, 2H; Ar- H-3, Ar- H-11), 7.25(m, 2H: Ar-H-1, Ar-H-9), $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 27.10 (C-5, C-13), 28.90 (C-7, C-15), 31.20 (C-6, C-14), 34.70(C-8, C-16), 124.00(C-8', C-16'), 125.90 (C-2, C-10), 127.00(C-3, C-11), 127.30 (C-6', C-14'), 127.60(C-1, C-9), 127.70 (C-4, C-12), 137.50 (C-1', C-9'), 138.30 (C-4', C-12'). MS(m/z (rel.%)): m/z 312 (M^+ , 62 %), 284 (100%), 180 (50%), 166(36%), 156(12%), 142(10%), 128(12%). UV (CHCl_3) λ_{\max}/nm (log ϵ): 262.4 (3.7613). Analysis calc. for $\text{C}_{24}\text{H}_{24}$: C, 92.26; H, 7.74. Found: C, 92.22; H, 7.71.

2,10-dimethyl-5,6,8,13,14,15,16-octahydrocycloocta[1,2-*a*:5,6-*a'*] dinaphthalene (XVII):

Colourless oil (68.5%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3050-3100 (v Ar-C-H), 2840-2930 (v C-H), 1604 (v C=C), 1500, 1447 (v C-H), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 2.00 (s, 8H; H-7, H-8, H-15, H-16), 2.29 (t, 4H; H-6, H-14), 2.35 (s, 6H; Ar-CH₃), 2.59 (t, 4H; H-5, H-13), 6.89 (d, 2H: Ar-H-3, Ar-H-11), 6.95 (d, 2H; Ar-H-4, Ar- H-12), 7.05 (s, 2H: Ar- H-1, Ar-H-9), $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 24.70 (Ar- Me), 26.80 (C-7, C-15), 29.10 (C-5, C-13), 31.20 (C-6, C-14), 31.70 (C-8, C-16), 124.00 (C-6', C-14'), 126.60 (C-1, C-9), 127.30 (C-8', C-16'), 127.60 (C-4, C-12) 128.20 (C-3, C-11), 132.23 (C-4', C-12'). 135.50 (C-2, C-10), 137.4 (C-1', C-9'), MS(m/z (rel.%)): 340 (M^+ , 34 %), 326 (16%), 298 (32%), 284 (58 %), 271 (100%), 270 (50%) 257 (64%), 256 (58%), 242 (20%), 214 (12%), 104 (24 %). UV (CHCl_3) λ_{\max}/nm (log ϵ): 273 (3.8202). Analysis calc. for $\text{C}_{26}\text{H}_{28}$: C, 91.71; H, 9.29. Found: C, 91.65; H, 8.32.

5,6,7,8,13,14,15,16-octahydro-2,3,10,11-tetramethylcycloocta[1,2-*a*:5,6-*a'*] dinaphthalene (XVIII)

Colourless oil (62.5%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3100 (v Ar Str.), 2850-2940 (v C-H), 1620 (v C=C), 1600 (v Ar-H), 1460 (v C-H), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 2.29 (t, 4H; H-6, H-14), 2.59 (t, 4H; H-5, H-13), 2.00 (s, 8H; H-7, H-8, H-15, H-16), 6.97 (t, 2H; Ar-H-2, Ar- H-10), 7.13 (d, 2H; Ar-H-1, Ar-H-9), $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 20.00 (C-5, C-13), 26.80 (C-7, C-15), 30.70 (C-6, C-14), 31.70 (C-8, C-16), 124.00 (C-6', C-14'), 124.40 (C-1, C-11), 125.28 (C-2, C-10), 127.30 (C-8', C-16'). 128.00 (C-3, C-9), 133.00 (C-4, C-12), 138.30 (C-4', C-12'), 138.90 (C-1', C-9'), MS(m/z (rel.%)): 380 (M^+ +2, 25 %), 366 (26%), 289 (100 %). 273 (3.8812) 270 (12%), 228 (14%), 214 (14%), 191 (100%), 184 (10%), 156 (38%), 104 (38 %), 103 (10%). UV (CHCl_3) λ_{\max}/nm (log ϵ): 272 (3.9236), Analysis calc. for $\text{C}_{28}\text{H}_{32}$: C, 91.25; H, 8.75. Found: C, 91.29; H, 8.75.

4,12-dichloro-5,6,7,8,13,14,15,16-octahydrocycloocta[1,2-*a*:5,6-*a'*]dinaphthalene (XIX)

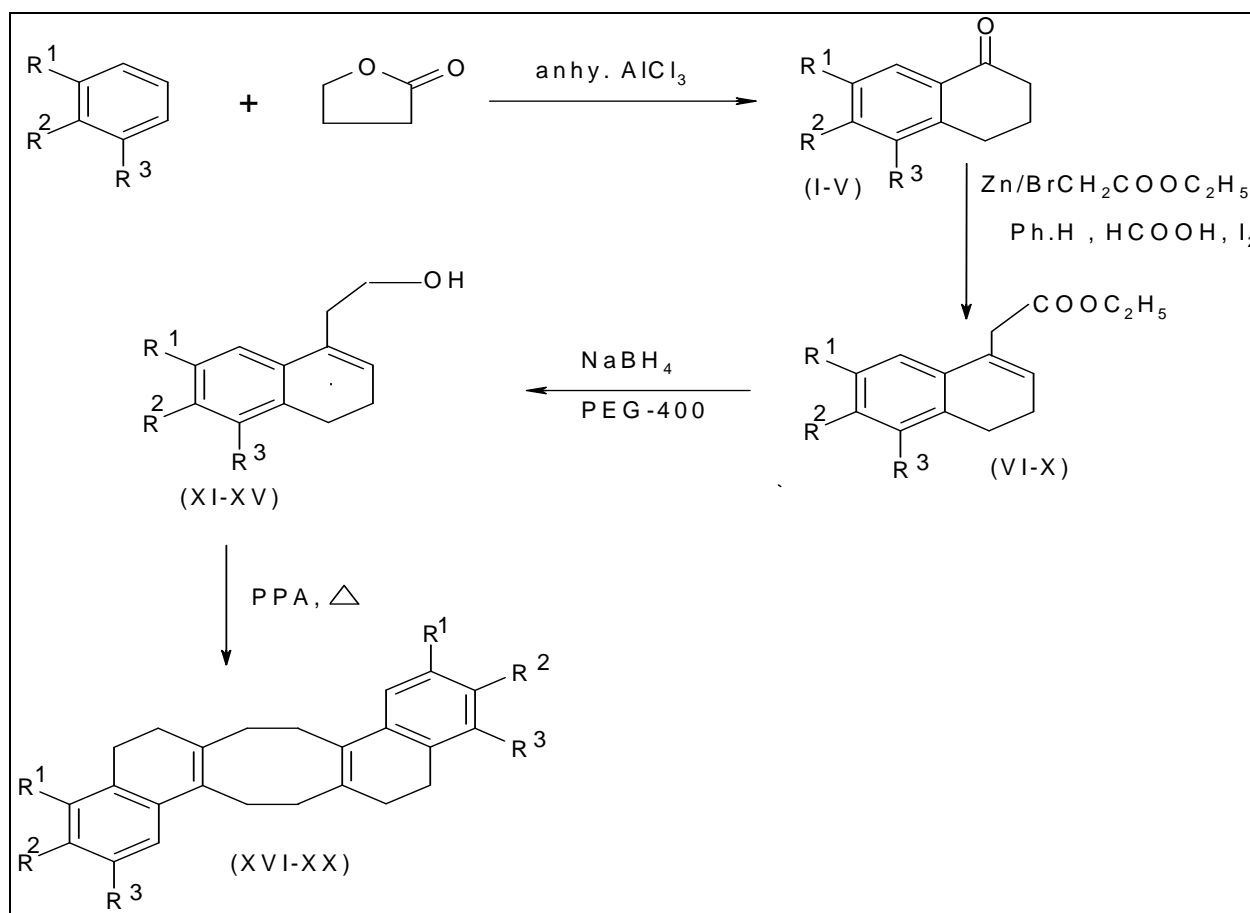
Colourless oil (60.8%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3100 (v Ar Str.), 2850-2940 (v C-H), 1620 (v C=C), 1600 (v Ar-H), 1460 (v C-H), $^1\text{H-NMR}$ (CDCl_3 , 300MHz): δ 2.29 (t, 4H; H-6, H-14), 2.59 (t, 4H; H-5, H-13), 2.00 (s, 8H; H-7, H-8, H-15, H-16), 6.97 (t, 2H; Ar-H-2, Ar- H-10), 7.13 (d, 2H; Ar-H-1, Ar-H-9). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 20.00 (C-5, C-13), 26.80 (C-7, C-15), 30.70 (C-6, C-14), 31.70 (C-8, C-16) 124.00 (C-6', C-14'), 124.40 (C-1, C-11), 125.28 (C-2, C-10), 127.30 (C-8', C-16'). 128.00 (C-3, C-9), 133.00 (C-4, C-12), 138.30 (C-4', C-12'), 138.90 (C-1', C-9'), MS(m/z (rel.%)): 380 (M^+ +2, 25 %), 366 (26%), 289 (100 %). 273 (3.8812) 270 (12%), 228 (14%), 214 (14%), 191 (100%), 184 (10%), 156 (38%), 104 (38 %), 103 (10%). UV (CHCl_3) λ_{\max}/nm (log ϵ): 272 (3.8812). Analysis calc. for $\text{C}_{24}\text{H}_{22}\text{Cl}_2$: C, 75.59; H, 5.81, Cl, 18.59. Found: C, 75.54; H, 5.78, Cl, 18.67.

5,6,7,8,13,14,15,16-octahydro-2,10-dipropylcycloocta[1,2-*a*:5,6-*a'*] dinaphthalene (XX)

Colourless oil (25%), IR (oil film) $\nu_{\max}/\text{cm}^{-1}$: 3005-3100 (v Ar- C-H Str.), 2860-2940 (v Ali. C-H Str.), 1600 (Ar-Str.), 1590 (v C=C), 1500 (v C-H), 1460 (v C-H), $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 1.29 (s, 12H; C(CH₃)₂), 2.29 (t, 4H; H-6, H-14), 2.59 (t, 4H; H-5, H-13), 2.00 (s, 8H; H-7, H-8, H-15, H-16) 3.12 (m, 2H; H-17, H-18), 7.12 (s, 2H; Ar- H-1, Ar- H-9), 6.96 (d, 2H; Ar- H-3, Ar- H-11), 6.99 (m, 2H; Ar- H-4, Ar- H-12). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ

18.06 (C-19, C-20, C-21, C-22), 18.90 (C-6, C-14), 19.60 (C-5, C-13), 21.01 (C-17, C-18), 24.06 (C-7, C-15), 26.09 (C-8, C-16), 121.09 (C-1, C-9), 124.32 (C-3, C-11), 126.25 (C-4, C-12), 130.81 (C-8', C-16'), 132.26 (C-6', C-14'), 134.13 (C-4', C-12'), 138.07 (C-1', C-9'), 145.24 (C-2, C-10). MS(m/z(rel.%)): 396 (M⁺, 44 %), 382 (10%), 214 (14%), 198 (18%), 170 (18%), 130 (84 %), 131 (100%), 104 (8 %). UV (CHCl₃)λ_{max}/ nm (log ε): 271.4 (3.7810). Analysis calc. for C₃₀H₃₆: C, 90.85; H, 9.15. Found: C, 90.89; H, 9.12.

Scheme



Compounds	R ¹	R ²	R ³
I, VI, XI, XVI	H	H	H
II, VII, XII, XVII	CH ₃	H	H
III, VIII, XIII, XVIII	CH ₃	CH ₃	H
IV, IX, XIV, XIX	H	H	Cl
V, X, XV, XX	CH(CH ₃) ₂	H	H

CONCLUSION

We have developed a short synthesis of 8-membered macrocycles, having the carbocyclic framework of diterpenoids by utilizing easily available and inexpensive chemicals.

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