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GENERAL APPROACH FOR THE STEREOCONTROLLED SYNTHESIS OF TRICYCLIC LACTONES VIA ALLENE INTRAMOLECULAR CYCLOADDITION. AN APPLICATION TO THE SYNTHESIS OF (±)-PLATYPHYLLIDE

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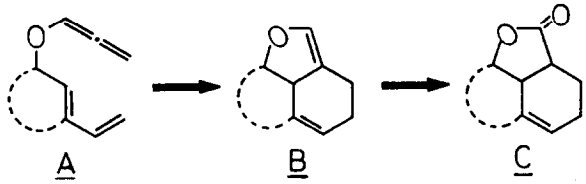
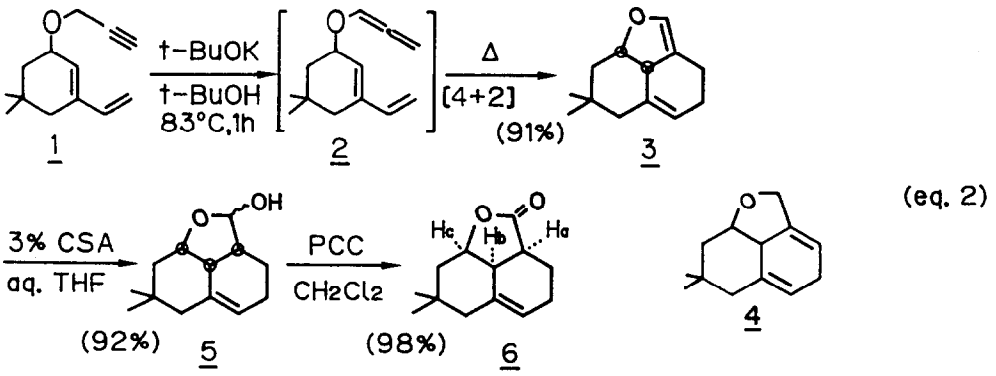
Abstract: A new synthesis of tricyclic lactones via allene intramolecular cycloaddition and its application to synthesis of (±)-platyphyllide are described.

The polycyclic fused lactone system is one of the fundamental building blocks of a large number of naturally occurring terpenoid compounds,[1] some of which have been of great interest owing to their diverse biological activities.[2] Herein we wish to report on a new development of facile synthesis of tricyclic lactone systems (C) based on the intramolecular Diels-Alder reactions of the allenyl ethers (A) followed by hydration and oxidation of the resulting adducts (B) as outlined in eq 1.



(eq.1)

Recently, we have found that the allenyl ether undergoes the intramolecular Diels-Alder reaction with extraordinary ease due to its favorable geometry.[3,4] This strategy is now successfully utilized in the synthesis of the tricyclic lactones. Thus, when the propargyl ether 1[5,6] was heated in t-BuOH (83 °C) in the presence of t-BuOK (excess) for 1 h, adduct 3[7] was obtained as the sole product in 91% yield via the allenyl ether intermediate 2, whereas direct heating of 1 in benzene (80 °C, 7 h) afforded the isomeric adduct 4 (90%) (eq 2). While 4 was stable and recovered unchanged, treatment of 3 with 3% solution of 10-camphorsulfonic acid (CSA) in THF/H_2O (30:1) at room temperature for 30 min gave a 92% yield of lactol 5[6] which was readily oxidized by PCC in CH_2Cl_2 to give lactone 6[8] in 98% yield. The cis ring fusion of lactone in 6,



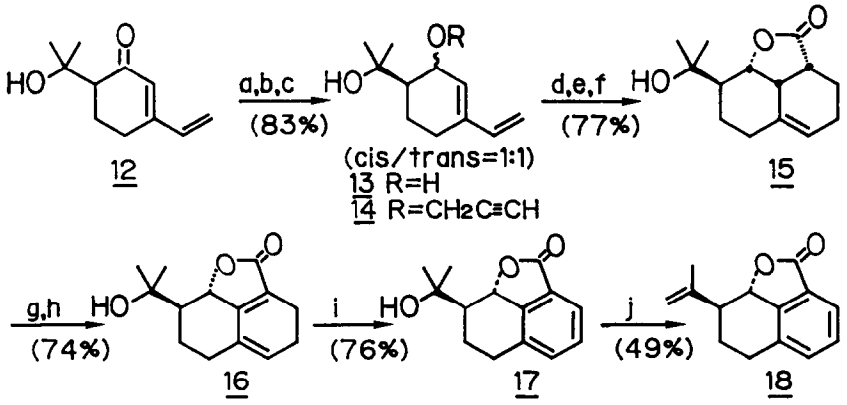
(eq. 2)

confirmed by the ^{1}H NMR spectrum using the shift reagent (Eu(dpm)$_3$),[8] can be attributed to the stereospecific cycloaddition of 2 as well as hydration of 3.

Table I shows the results of the lactone synthesis for other substrates. The base-catalyzed intramolecular cycloaddition proceeded smoothly at 83 °C and the dihydrofuran products obtained were converted into the corresponding lactones in high yieds except for the acid labile 7. Compound 8 (entry c) was considered to be derived from the thermal product (like 4) via aromatization, since 7 gave no 8 under the same reaction conditions. In entry d, the milder reaction at 40 °C led to the isolation of the 'allene' intermediate (11) which in turn underwent at 83 °C a rapid cylcization with concomitant hydrogen shift to give 10, while the direct heating of 9 resulted in no reaction at all.

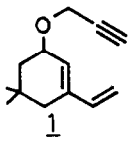
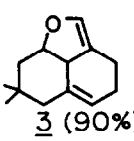
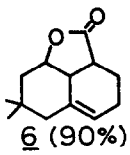
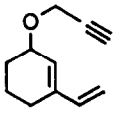
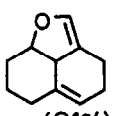
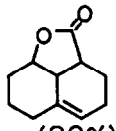
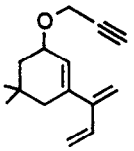
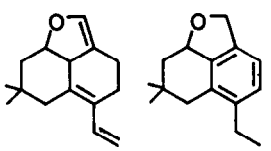
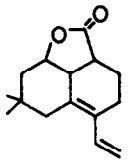
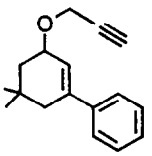
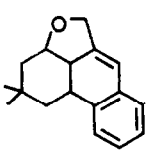
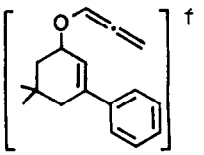
The synthetic utility of this methodology was shown by the application to the synthesis of the norsesquiterpene lactone, platyphyllide (18)[9] (Scheme I).[6] The low-temperature reduction (-110 °C) of aldol 12, prepared by the reaction of 3-vinylcyclohexanone and actone, gave a 1:1-stereoisomeric mixture of diol 13 which were directly propargylated without isolation, since the chromatographic separation and identification of each stereoisomer could be much easily

Scheme I[a]



[a](a) LAH,Et2O,-110°C: (b) n-BuLi,C6H6,DMSO,then CH≡CCH2Br: (C) SiO2-chromatography: (d) t-BuOK,t-BuOH,83°C: (e) CSA,THF,H2O: (f) PCC,CH2Cl2: (g) LDA,THF,then PhSeCl: (h) 30%H2O2,CH2Cl2: (i) DDQ,C6H6: (j) SOCl2,Py,0°C

Table I. Lactone Syntheses via Allene Intramolecular Cycloaddition and Hydration-Oxidation Procedures [a]

entry	starting [b] material	cycloadduct [c] (yield,%) [e]	hydration-oxidation [d] product (yield,%) [e]
a	 1	 3 (90%)	 6 (90%)
b		 (81%)	 (89%)
c		 7 (65%) 8 (22%)	 (11%)
d	 9	 10 (76%)	 [f] 11

[a] See ref.6. [b] See ref.5. [c] Unless otherwise noted, all reactions were carried out in t-BuOH at 83°C in the presence of 2 equiv. of t-BuOK. [d] See the text. [e] Isolated yields. [f] Isolated in the reaction at 40°C in the presence of t-BuOK.

achieved in 14.[10] The desired trans isomer of 14 (more polar) was subjected to the above lactone synthesis, giving lactone 15 as the sole product in 77% overall yield. The phenylselenation followed by oxidative elimination gave the diene 16 which was readily dehydrogenated by DDQ[11] to give 17.[9] The dehydration of 17 by the method of Bohlmann[9] afforded (±)-platyphyllide 18[12] which is identical with the authentic sample in all spectral aspects.[13] The cis isomer of 18 was also synthesized similarly using the corresponding cis isomer of 14.

This unique lactone synthesis is characterized by a very facile and stereospecific formation of tricyclic ring system under the mild reaction conditions and bears a ppotential utility for the synthesis of the related polycyclic systems seen in many natural products.

References and Notes

1. J. S. Glasby, "Encyclopedia of the Terpenoids"; Wiley: New York, 1982.
2. For example, see: Y. Hayashi, T. Matsumoto, T. Tashiro, Gann, 1979, 70, 365, and references cited therein.
3. K. Hayakawa, M.Yodo, S.Ohsuki, K. Kanematsu, J.Am.Chem.Soc. 1984, 106, 6735.
4. K. Hayakawa, Y. Yamaguchi, K.Kanematsu, Tetrahedron Lett. 1985, 26, 2689.
5. The requisite propargyl ethers (ex., 1) were readily prepared from the corresponding 3-vinylcyclohexenones by successive treatments; 1) $NaBH_4$, $CeCl_3$, MeOH; 2) n-BuLi, DMSO, C_6H_6, then $CH{\equiv}CCH_2Br$.
6. Satisfactory spectroscopic data were obtained for all new compounds.
7. 3: ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H), 0.98 (s, 3H), 1.53 (d, J = 6.0 Hz, 2H), 1.84 (m, J = 6.0 Hz, 2H), 2.09-2.53 (m, 4H), 3.14 (dm, J = 10.0 Hz, 1H), 4.68 (dt, J = 10.0, 6.0 Hz, 1H), 5.14-5.37 (m, 1H), 5.97 (m, 1H); IR (neat) 1650, 1080 cm^{-1}; MS m/z 190 (M^+, 100%), 161 (38%), 136 (96%). 4: ^1H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.01 (s, 3H), 1.61 (dd, J = 14.0, 9.0 Hz, 1H), 1.49 (dd, J = 14.0, 4.5 Hz, 1H), 1.96 (br s, 2H), 2.50-3.05 (m, 3H), 4.28 (br s, 2H), 4.32 (td, J = 9.0, 4.5 Hz, 1H), 5.51 (m, 1H), 5.75 (m, 1H); IR (neat) 1055, 1035 cm^{-1}; MS m/z 190 (M^+, 34%), 105 (81%), 91 (100%).
8. 6: ^1H NMR δ 0.82 (s, 3H), 0.98 (s, 3H), 1.50 (dd, J = 14.5, 2.3 Hz), 2.03 (dd, J = 14.5, 2.3 Hz, 1H), 1.70-2.40 (m, 6H), 2.76 (ddm, J =4.5, 3.0 Hz, 1H), 2.90 (ddd, J = 7.0, 4.5, 3.0 Hz, 1H), 4.55 (td, J = 4.5, 2.3 Hz, 1H), 5.57 (m, 1H); $\Delta\delta$[ppm]/Eu(dpm)$_3$[mol%] = 0.050 (Ha), 0.029 (Hc), 0.022 (Hb); IR ($CHCl_3$) 1760, 1170 cm^{-1}; MS m/z 206 (M^+, 68%), 161 (98%), 91 (100%).
9. Isolation: F. Bohlmann, K.H. Knoll, C. Zdero, P.K. Mahanta, M. Grenz, A. Suwita, D. Ehlers, N. LeVan, W.R. Abraham, A.A. Natu, Phytochemistry, 1977, 16, 965. Synthesis; F. Bohlmann, E. Eickeler, Chem. Ber. 1979, 112, 2811.
10. ^1H NMR δ ($CDCl_3$): cis-14; 1.08-1.60 (m, 1H), 1.25 (s, 3H), 1.38 (s, 3H), 1.6-2.3 (m, 4H), 2.46 (t, J = 2.4 Hz, 1H), 3.22 (br s, D_2O-exchange, 1H), 4.25 (d, J = 2.4 Hz, 2H), 4.52 (dd, J = 5.4, 3.0 Hz, 1H), 5.10 (d, J = 10.8 Hz, 1H), 5.28 (d, J = 17.4 Hz, 1H), 5.98 (d, J = 5.4 Hz, 1H), 6.39 (dd, J = 17.4, 10.8 Hz, 1H). tans-14; 1.20-1.60 (m, 1H), 1.22 (6H, s), 1.60-2.08 (m, 2H), 2.1-2.4 (m, 2H), 2.49 (t, J = 2.4 Hz, 1H), 4.04 (br s, D_2O-exchange, 1H), 4.29 (d, J = 2.4 Hz, 2H), 4.30-4.60 (m, 1H), 5.07 (d, J = 10.8 Hz, 1H), 5.18 (d, J=18.0 Hz, 1H), 5.77 (br s, 1H), 6.39 (dd, J = 18.0, 10.8 Hz, 1H).
11. In the case of over-dehydrogenation to the styrene derivative, its catalytic hydrogenation over Pd/C (quantitative yield) to 17 was required.
12. Compound 18; mp 65.0-67.0 °C, ^1H NMR (100 MHz) δ 1.90 (d, J = 1.0 Hz, 3H), 1.70-2.20 (m, 3H), 2.82 (dt, J = 17.0, 8.0 Hz, 1H), 3.18 (dd, J = 17.0, 8.0 Hz, 1H), 4.98 (d, J = 1.0 Hz, 2H), 5.23 (d, J = 10.3 Hz, 1H), 7.25-7.50 (m, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.68 (ddm, J = 8.0, 1.7 Hz, 1H); IR ($CHCl_3$) 1765, 1100, 1000 cm^{-1}; MS m/z 214 (M^+, 34%), 146 (89%), 118 (100%).
13. We are grateful to Prof. F. Bohlmann for the private communication concerning spectral properties as well as biological activities of 18.

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