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A HIGHLY EFFICIENT SYNTHESIS OF BICYCLO[n.3.1] RING SYSTEMS BY ALLENE INTRAMOLECULAR CYCLOADDITION: TANDEM INTRAMOLECULAR [2+2] CYCLOADDITION-[3,3]-SIGMATROPIC REARRANGEMENT

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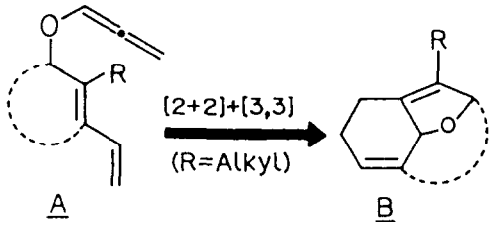
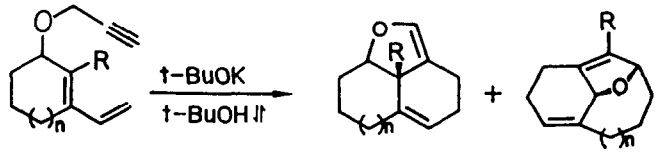
Abstract: A novel one-step construction of bicyclo[5.3.1]undecane skeleton via intramolecular cycloaddition of allenyl ethers is described.

The intramolecular cycloadditions of allenes[1] constitute the versatile methods for the stereocontrolled synthesis of variously functionalized polycyclic compounds.[2-4] In particular, its intramolecular Diels-Alder reactions fully enjoy the merits of the unique structure of allenes and proceed with extraordinary ease.[4,5] As a part of our studies on development of the general and efficient synthetic methods due to the allene cycloaddition strategy,[4] we report herein a new approach to the facile construction of tricyclic [n.3.1] carbon ring systems (**B**) via the novel tandem intramolecular [2+2] cycloaddition and [3,3]-sigmatropic rearrangement of the allenyl ethers (**A**) as shown in eq 1.



A B (1)

While thermal treatment of the propargyl ether **1a** (R = H) with t-BuOK led to a smooth formation of Diels-Alder adduct **2a** via the allenyl ether intermediate,[4c] **1b**[4e] (R = Me) was found to undergo a quite different kind of rearrangement with remarkable ease. Thus, when a solution of **1b** in t-BuOH was heated at 83 °C in the presence of t-BuOK (8 equiv), **1b** was rapidly consumed (30 min) and the novel adduct **3b** was obtained as a sole product in 88% yield (eq 2). The structure of **3b** was confirmatively determined by the spectroscopic data [MS m/e 176 (M^+); ^{1}H NMR ($CDCl_3$) δ 5.27 (m, H-8), 4.97 (small m, H-3), 4.82 (br s, H-11), 1.48 (s, CH_3); ^{13}C NMR δ 153.10 (s, C-1), 138.24 (s, C-7), 125.14 (s, C-2), 116.30 (d, C-8), 88.75 (d, C-11), 85.88 (d, C-3)] as well as the chemical transformations. Catalytic hydrogenation of **3b** (1 atm H_2, 5% Pd-C, EtOH) gave the dihydro-derivative **4**[6] [m/e 178 (M^+)] and its oxidation with *m*-CPBA (CH_2Cl_2, 0 °C) afforded the monoepoxide **5**[6] (overall 57%) [MS m/e 194 (M^+); ^{1}H NMR δ 4.18 (d, $J_{11,7}$ = 6.5 Hz, H-11)], whereas treatment of **3b**

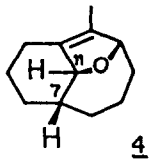


(2)

1a, R=H (n=1)
b, R=Me (n=1)
c, R=Me (n=0)

2a (81%)
b, (-)
c, (60%)

3a, (-)
b, (88%)
c, (30%)



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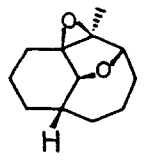

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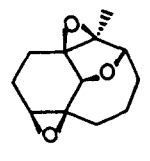

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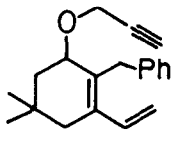

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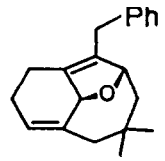
(92%)



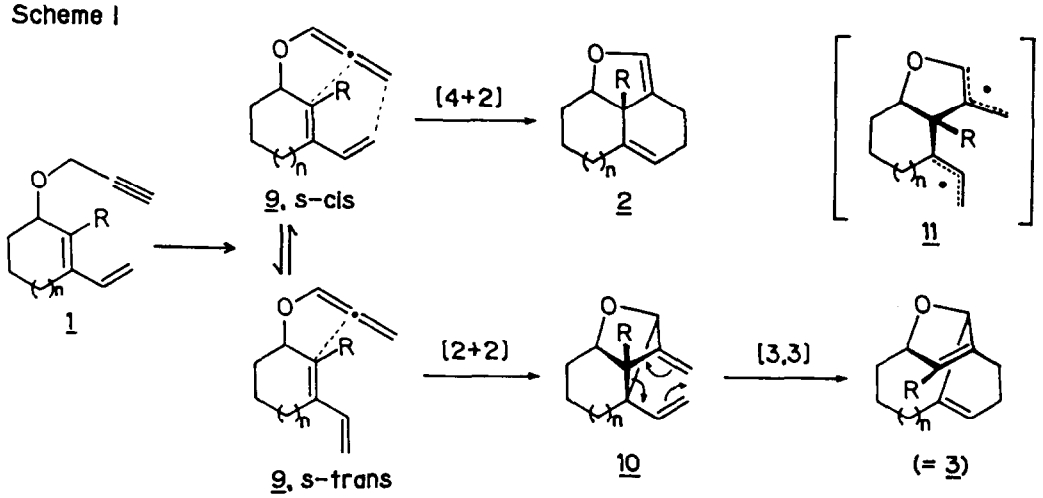
8

(3)

with m-CPBA (2 equiv) produced the crystalline diepoxide 6[6] (91%): mp 95-96 °C; MS m/e 208 (M^+); ^{1}H NMR δ 3.94 (s, H-11). This novel reaction generally occurred when the C-2 position in 1 was displaced by the sterically demanding substituent (R). For example, the similar base treatment of 7[4e] resulted in a smooth rearrangement to give 8[6] in 92% yield (eq 3). However, the reaction of cyclopentene derivative 1c gave a mixture of 3c (30%) and Diels-Alder adduct 2c (60%) (eq 1).[4c,6,9]

The formation of these new products (3 and 8) can be most reasonably explained by successive [2+2] cycloaddition of the initially formed allenyl ether 9[4,7] to 10 and its [3,3]-sigmatropic rearrangement (Cope rearrangement),

Scheme I



1

9, s-cis

2

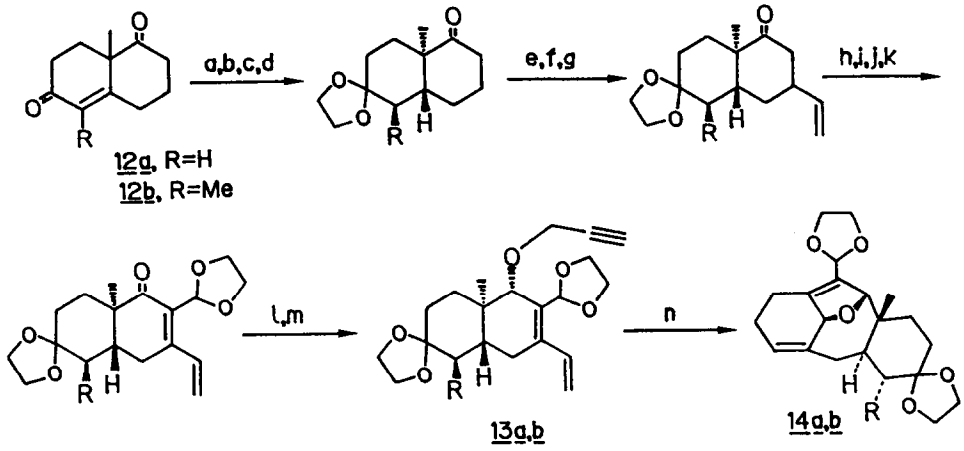
11

9, s-trans

10

(= 3)

Scheme II[a]



[a]Reaction conditions (yield; a, b): (a) $NaBH_4$, EtOH, 0°C (83%, 84%); (b) Li, liq NH_3 (54%, 75%); (c) $(CH_2OH)_2$, p-TsOH, C_6H_6, Dean-Stark, 80°C (99%, 95%); (d) PCC, CH_2Cl_2 (95%, 91%); (e) LDA, THF, -78°C, then PhSeCl (89%, 93%); (f) 15% H_2O_2, Py, CH_2Cl_2,0°C (77%, 83%); (g) CuI, $CH_2CHMgBr$, THF, -78°C (81%, 92%); (h) NaH, THF, 0°C, then HCO_2Et (93%, 78%); (i) [= (c)] (60%, 75%); (j) [= (e)] (45% at 55% conversion, 38% at 43% conversion); (k) [= (f)] (100%, 96%); (l) for a, $NaBH_4$, $CeCl_3$, MeOH, 0°C (46%); for b DIBAL-H, C_6H_6, 5°C (58%); (m) n-BuLi, DMSO, C_6H_6, 0°C, then $CHCCH_2Br$ (51%, 54%); (n) t-BuOK (8 equiv), t-BuOH, 83°C (100%, 96%).

in which the sterically most compressed C_2-C_3 bond is preferentially cleaved to give 3 (Scheme I). The remarkable change of reaction mechanism can be attributed to the steric effects of the C-2 substituent (R). The bulky R would sterically disfavor the s-cis conformation of 9 which is necessitated for the [4+2] reaction leading to 2, whereas the [2+2] cycloaddition of 9 is considered to occur by the sterically less demanding stepwise mechanism via the diradical intermediate 11.[8]

The above new synthesis of bicyclo[n.3.1] ring systems based on the tandem intramolecular [2+2] cycloaddition-[3,3]-sigmatropic rearrangements of allenyl ethers may be characterized by special advantages including procedual simplicity, mildness of the reaction conditions, high efficiency, and the predictable stereochemistry of the product. Finally, the synthetic utility of this new method was demonstrated by a facile construction of tricyclic[$9.3.1.0^{4,9}$]-pentadecane skeleton, characteristic of the taxane diterepenes.[10] Thus, treatment of the bicyclic propargyl ethers 13a,b, prepared from the Wieland-Miesher ketones (12a,b) as shown in Scheme II, with t-BuOK (8 equiv) in t-BuOH at 83 °C for 1 h afforded 14a,b[10] in almost quantitative yields.[11] Further studies on synthesis of taxane derivatives using this strategy are now in progress.

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6. All new compounds gave satisfactory analytical and/or spectral data. For example, **3c**: ^{13}C NMR q [δ 10.237], t [19.890, 22.874, 27.788, 29.017], d [82.195, 84.535, 115.542], s [119.871, 141.634, 147.542]. **4**: ^{13}C NMR q [δ 9.360], t [21.704, 23.400, 24.863, 2x28.900, 33.053], d [42.823, 85.881, 89.099], s [130.343, 131.454]; MS m/e 178 (M^+). **5**: ^{1}H NMR δ 1.43 (s,3H), 4.05 (d, J=6.5 Hz, 1H), 4.18 (dm, J=5.9 Hz, 1H); ^{13}C NMR q [δ 11.404], t [20.030, 22.613, 25.147, 29.582, 30.703, 31.239], d [38.696, 79.342, 80.609], s [68.182, 68.523]; MS m/e 194 (M^+). **6**: mp 95-96°C, ^{1}H NMR δ 1.39 (s,3H), 3.06 (dd, J=5.0, 6.0 Hz, 1H), 3.95 (s, 1H), 4.26 (m, 1H); ^{13}C NMR q [δ 11.355], t [20.859, 21.200, 23.783, 30.752, 33.140], d [57.703, 78.660, 80.219], s [63.308, 66.281, 68.523]; MS m/e 208.1109 (calcd for $C_{12}H_{16}O_3$, 208.1099). **8**: ^{13}C NMR q [δ26.658, 34.554], t[20.469, 23.637, 32.312, 45.812 46.055], d [85.873, 86.311, 118.867, 126.080, 4 x 128.420], s [129.442, 138.411, 145.965, 155.858. **14a**: ^{13}C NMR q [δ 10.062], t [17.316, 26.092, 30.538, 32.761, 36.739, 38.143, 2 x 64.352, 64.820, 65.639], d [34.750, 89.625, 106.474, 124.376, 136.778], s [53.471, 2 x 108.93, 113.962, 134.204]. **14b**: mp 123-125 °C; ^{1}H NMR δ 0.84 (s,3H), 0.85 (d,J=6.0 Hz,3H), 1.30-2.00 (m,7H), 2.00-2.90 (m,5H), 3.70-4.30 (m,4H), 3.94 (s,4H), 4.16 (s, 1H), 4.83 (s, 1H), 5.50 (m, 1H), 6.11 (s, 1H); ^{13}C NMR q [δ 10.185, 11.111], t [17.301, 26.073, 30.313, 33.628, 36.357, 2 x 64.774, 65.111, 65.599], d [38.647, 41.279, 89.967, 106.440, 124.082, 136.754], s [36.990, 110.485, 113.896, 134.609];MS m/e 374.2105 (calcd for $C_{22}H_{30}O_5$, 374.2092).

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9. This may be attributed to the diminishing steric effect of R in **1c** due to the increased outer bond angle of the cyclopetene ring.

10. Several approaches to the taxane skeletons have been reported: (a) Holton, R.A. J.Am.Chem.Soc. **1984**, 106, 5731. (b) Nagaoka, H.; Ohsawa, K.; Takata, T.; Yamada,Y.; Tetrahedron Lett. **1984**, 25, 5389. (c) Shea, K.J.; Davis, P. D. Angew.Chem., Int.Ed.Engl. **1983**, 22, 419. (d) Sakan, K.; Craven, B.M. J. Am.Chem.Soc. **1983**, 105, 3732. (e) Brown, P.A.; Jenkins, P.R.; Facett, J.; Russell, D. R. J. Chem. Soc., Chem. Commun. **1984**, 253. (f) Ohtsuka, Y.; Ohishi, T. Tetrahedron Lett. **1986**, 27, 203 and references cited therein.

11. An X-ray crystallographic study for **14** has been unsuccessful, because of no availability of well-formed crystals at the present status.

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