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THE TANDEM CLAISEN-ENE REARRANGEMENT: A METHOD FOR THE STEREOCONTROLLED SYNTHESIS OF FUNCTIONALIZED CYCLOPENTANOIDS

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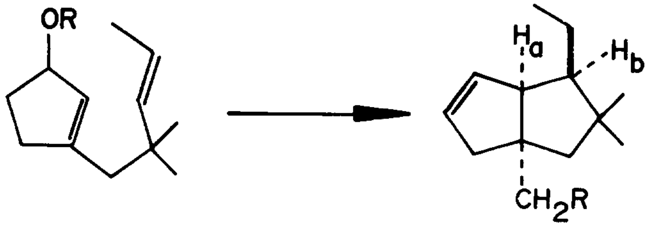
Abstract: The tandem Claisen-ene rearrangement is described. The presence of oxy-ene products is established.

We have previously described the tandem Cope-Claisen rearrangement and have applied it to the synthesis of pseudoguaianolides and steroids.[1] We describe in this Letter the Claisen rearrangement and ene reaction applied in tandem and report the presence of oxy-ene products during the course of the rearrangement of vinyl ether substrates and the reaction's potential for rapid assembly of functionalized [3.3.0] bicyclo-octanes.



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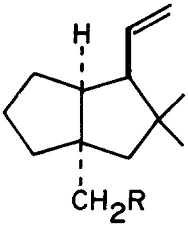

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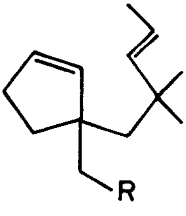

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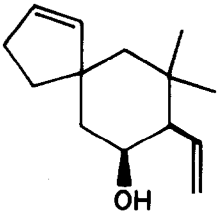

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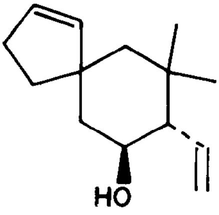

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a, R = H, b, R = CH=CH$_2$, c, R = CONMe$_2$, d, R = CHO

Thermolysis[2] (330°C, 2 h) of vinyl ether 1b provided a 1:1 mixture of aldehydes 2d and 3d (75%).[3,4] The separated isomers were submitted to sequential reduction ($LiAlH_4$, Et_2O), and hydrogenation to afford the same perhydro alcohol, requiring the isomers to be stereochemically equivalent.[5] The endo configuration of the ethyl group in aldehyde 2d was revealed by the appearance of H_a at δ 3.02 ($J_{a,b}$ = 9 Hz).[4] Reduction of the reaction time to one-half hour, revealed the presence of the two carbon-ene products 2d and 3d in addition to two oxy-ene products 5 and 6 in a ratio of 1.0/1.0/0.9 (2d/3d/5+6). When the thermolysis was conducted at 250°C (0.5 h) the Claisen aldehyde 4d appeared in the reaction mixture along with the four ene products (2d/3d/5+6/4d = 1.0/1.1/7.7+9.5/5.4). Hydrogenation of the separated alcohols 5 and 6 provided isomeric alcohols requiring the difference between 5 and 6 to lie in their respective stereochemistries and not the regiochemistry of the olefins. Alcohol 5 displayed its hydroxyl methine hydrogen as a multiplet at δ 4.03. Deuterium oxide exchange revealed the signal as a doublet (J = 11.8 Hz) of triplets (J = 4.5 Hz), requiring a cis arrangement of the hydroxyl and vinyl group. On the other hand, the same resonance in alcohol 6 (δ 3.68) appeared as a triplet (J = 10.9 Hz) of doublets (J = 4.0 Hz) without deuterium exchange.[6]

The presence[7] of the oxa-ene products in the tandem reaction was further demonstrated by subjecting a mixture of alcohols 5 and 6 to thermolysis (330°C, 2 h) thereby providing the carbon-ene products 2d and 3d in a 1:1 ratio.

The Claisen rearrangement could be insulated from the ene reactions by low temperature thermolysis (200°C, 0.5 h) of 1b, thereby providing the aldehyde 4b as the sole product of the reaction.

Thermolysis (330°C, 0.5 h) of alcohol 1a in the presence of dimethylacetamide dimethylacetal (DMADA) afforded a mixture of regioisomeric olefinic amides 2c and 3c in a 1:1 ratio (18%). Hydrogenation of the separated isomers once again gave a single perhydro derivative. The low yield in the tandem reaction was attributed to the Claisen rearrangement. Upon refluxing a solution of alcohol 1a in the presence of DMADA (xylene, 144°C, 6 h) the amide 4c was obtained in 26% yield. Submission of this intermediate of the tandem reaction to thermolysis (330°C, 0.5 h) gave rise to the same mixture of amides in 85% yield.

Further studies in this area concerning the effect of ring substituents and chain olefin geometry are under investigation.

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REFERENCES AND NOTES:

1. F. E. Ziegler and J. J. Piwinski, J. Am. Chem. Soc., 104, 7181 (1982); F. E. Ziegler, J.-M. Fang, and C. C. Tam, ibid., 104, 7174 (1982); F. E. Ziegler and H. Lim, J. Org. Chem., 47, 5229 (1982).
2. Samples were sealed at 0.2 mm in heavy wall pyrex tubes after several freeze-pump-thaw cycles.
3. All new compounds gave correct spectroscopic and/or combuston data. NMR data (270 MHz, CDCl$_3$): 1a, δ 0.99 (3H, s), 1.00 (3H, s, 2.05-2.50 (7H, m), 1.66 (3H, dd, J = 5.9, 1.3 Hz), 4.91 (1H, m), 5.37 (1H, dq. J = 16.2, 3.8 Hz), 5.43-5.49 (2H, m). 1b, δ 0.99 (3H, s), 1.00 (3H, s), 1.81-2.50 (6H, m), 1.66 (3H, dd, J = 5.9, 1.1 Hz), 3.99 (1H, dd, J = 16.8, 1.6 Hz, 4.23 (1H, dd, J = 14.8, 1.5 Hz), 4.95 (1H, m), 5.31 (1H, dq, J = 15.5, 5.9 Hz), 5.42 (1H, dq, J = 15.5, 1.1 Hz), 5.51 (1H, m), 6.39 (1H, dd, J = 14.3, 6.7 Hz). 2c (partial, contaminated with 3c), δ 0.91 (s), 1.00 (s), 1.59 (d, AB, J = 13.5 Hz), 2.03 (d, AB, J = 13.5 Hz), 2.49 (m), 2.76 (ddd, J = 13.5, 5.4, 2.0 Hz), 2.98 (s), 5.58 (m), 5.72 (m). 3c, δ 0.95 (3H, s), 0.99 (3H, s), 1.65-2.55 (12H, m), 1.70 (1H, d, AB, J = 14.8 Hz), 1.85 (1H, d, AB, J = 14.8 Hz), 2.41 (1H, d, AB, J = 16.1 Hz), 2.47 (1H, d, AB, J = 16.1 Hz), 2.95 (3H, s), 3.01 (3H, s), 5.03 (1H, dd, J = 9.5, 2.7 Hz), 5.21 (1H, d, J = 16.2 Hz), 5.85 (1H, ddd, J = 16.2, 12.1, 9.5 Hz). 2d (partial, contaminated with 3d), δ 0.82 (s), 0.94 (s), 1.00 (t, J = 7.4

Hz), 1.59 (d, AB, J = 11.3 Hz), 1.83 (d, AB, J = 11.2 Hz), 2.53 (m), 3.02 (dt, J = 9.0, 3.7 Hz), 5.60 (m), 5.78 (m), 9.75 (t, J = 2.3 Hz). 3d, δ 0.97 (3H, s), 1.00 (3H, s), 1.45-2.42 (9H, m), 2.47 (2H, m), 2.54 (1H, dt, J = 8.1, 2.2 Hz), 5.02 (1H, dd, J = 8.10, 1.47 Hz), 5.07 (1H, m), 5.82 (1H, dt, J = 10.8, 8.1 Hz), 9.79 (1H, t, J = 2.6 Hz). 4a, δ 1.02 (3H, s), 1.04 (3H, s), 2.08-2.92 (6H, m), 1.66 (3H, dd, J = 6.1, 1.5 Hz), 2.47 (2H, m), 5.30 (1H, dq, J = 15.6, 6.0 Hz), 5.44 (1H, dq, J = 15.6, 1.33 Hz), 5.66 (1H, dt, J = 9.7, 2.2 Hz), 5.75 (1H, dt, J = 5.64, 2.10 Hz), 9.67 (1H, t, J = 3.0 Hz). 4c, δ 1.00 (3H, s), 1.02 (3H, s), 1.64 (3H, dd, J = 6.21, 1.5 Hz), 1.69-2.00 (4H, m), 2.28 (2H, m), 2.40 (1H, d, AB, J = 16.2 Hz), 2.46 (1H, d, AB, J = 16.2 Hz), 2.91 (3H, s), 2.92 (3H, s), 5.27 (1H, dq, J = 15.7, 6.3 Hz), 5.50 (1H, dq, J = 15.6, 1.5 Hz), 5.59 (1H, dt, J = 5.7, 2.3 Hz), 5.90 (1H, dt, J = 5.7, 2.1 Hz). 5, δ 0.87 (3H, s), 1.08 (3H, s), 2.15 (1H, dd, J = 10.4, 4.5 Hz), 4.03 (1H, m; shaken with D_2O: dt, J = 11.8, 4.5 Hz), 5.19 (1H, dd, J = 16.9, 2.2 Hz), 5.29 (1H, dd, J = 10.2, 2.3 Hz), 5.68 (1H, dt, J = 5.8, 2.3 Hz), 5.87 (1H, dt, 16.9, 10.3 Hz), 5.99 (dt, J = 5.8, 2.2 Hz). 6, δ 0.89 (3H, s), 0.96 (3H, s), 1.11-2.53 (10H, m), 3.68 (1H, td, J = 10.9, 4.0 Hz), 5.22 (1H, dd, J = 17.1, 2.1 Hz), 5.30 (1H, dd, J = 10.3, 2.1 Hz), 5.69 (1H, dt, J = 5.5, 2.4 Hz), 5.73 (1H, dt, J = 17.1, 10.0), 5.97 (1H, dt, J = 5.8, 2.1 Hz).

4. This ratio was not unexpected. See, W. Oppolzer, E. Pfenniger, and K. Keller, Helv. Chim. Acta., 56, 1807 (1973).
5. For a discussion of ene reaction transition states, see F. E. Ziegler and K. Mikami, this issue.
6. Although four diastereomeric oxy-ene products could be formed in principle, no evidence for additional isomers could be detected (GLC, 500 MHz ^{1}H NMR). The stereochemistry of the spirocenter in 5 and 6 could not be readily assigned.
7. W. Triebs and H. Schmidt, Berichte, 60, 2335 (1927); V. Grignard and J. Doeuvre, C. R. Acad. Sci., 190, 1164 (1930). See also, W. Oppolzer and V. Snieckus, Angew. Chem. Int. Ed. Eng., 17, 476 (1978).

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