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A New Stereocontrolled, Pyrylium-Based Route to Conjugated Dienynes: The First Synthesis of Carduusyne A

Patchanee Charoenying,[a] D. Huw Davies,[b] Darren McKerrecher[a] and Richard J. K. Taylor[a,*]

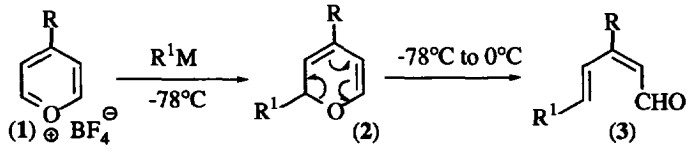
[a]Department of Chemistry, University of York, Heslington, York YO1 5DD, UK

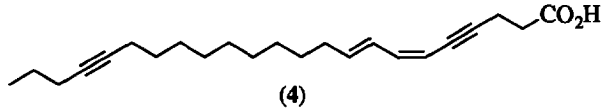
[b]Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

Abstract: A new stereocontrolled route to conjugated dienynes is described, utilising organometallic addition to pyrylium salts followed by Wittig homologation and dehydrohalogenation. The utility of this methodology is illustrated in the first total synthesis of the marine metabolite Carduusyne A.

There has been great interest in recent years in the design of stereocontrolled routes to enynes and dienynes.[1,2] As shown in Equation 1, we have developed the use of pyrylium salts (**1**) for the stereoselective synthesis of 2*Z*, 4*E*-dienals (**3a**),[3] and the corresponding 3-methyl derivatives (**3b**),[4] via the intermediate 2*H*-pyrans (**2**), and have utilised these compounds in natural product synthesis.[5] In this *Letter* we report the extension of the pyrylium methodology to the stereocontrolled preparation of 3*Z*, 5*E*-dienynes. We also describe the application of this new chemistry to the first synthesis of the recently isolated[6] marine metabolite Carduusyne A (**4**), an unusual twenty three carbon fatty acid which was characterised as the corresponding ethyl ester.

Equation 1 (a, R = H; b, R = Me)

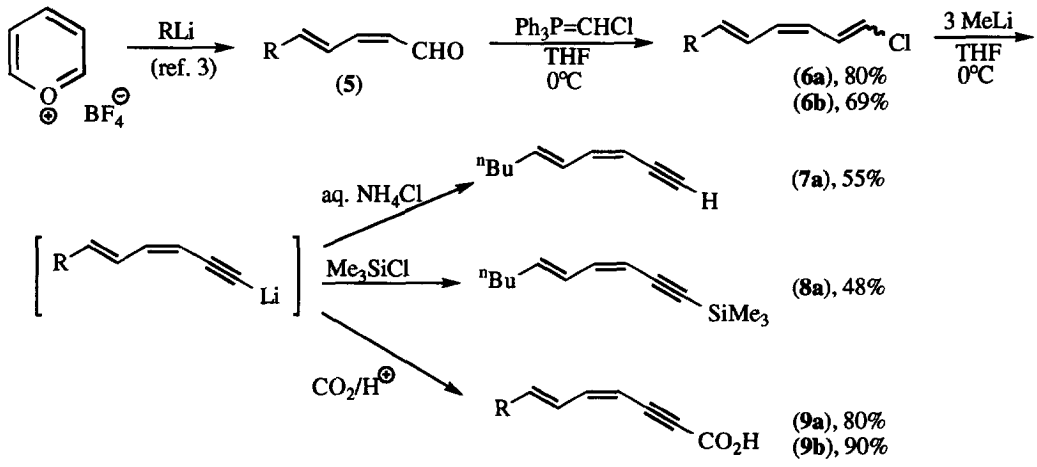




(4)

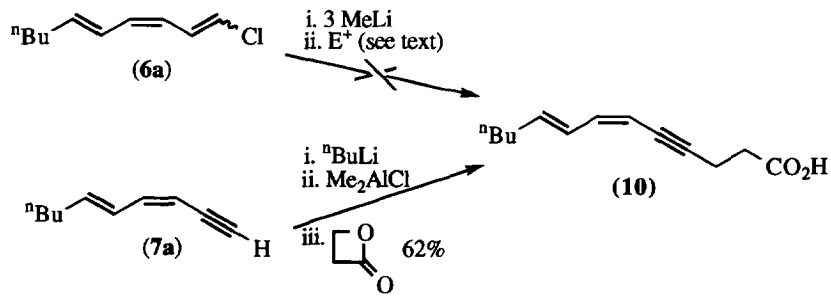
Model studies were carried out using dienals (**5a,b**) prepared from pyrylium tetrafluoroborate according to Equation 1.[3] Initial studies concentrated on the Corey-Fuchs homologation[7] (Ph_3P/CBr_4 then ^nBuLi) but, in our system, the intermediate vinyl dibromides rapidly decomposed, preventing further elaboration. The use of chloromethylene triphenylphosphorane,[8] however, proved successful giving vinyl chlorides (**6a,b**) in reasonable, unoptimised yields. Dropwise treatment of (**6a**) with excess methyllithium[9] followed by protonation or trimethylsilylation gave the expected products[10] (**7a**) and (**8a**) in 55% and 48% yields respectively (Scheme 1). The relatively low yields were ascribed to the volatility of (**7a**) and (**8a**) and therefore the intermediate lithio-alkynes were carboxylated to give dienyne acids (**9a**) and (**9b**) as single isomers[11] in high yields.

Scheme 1 (a, R = ^{n}Bu; b, R = ^{t}Bu)



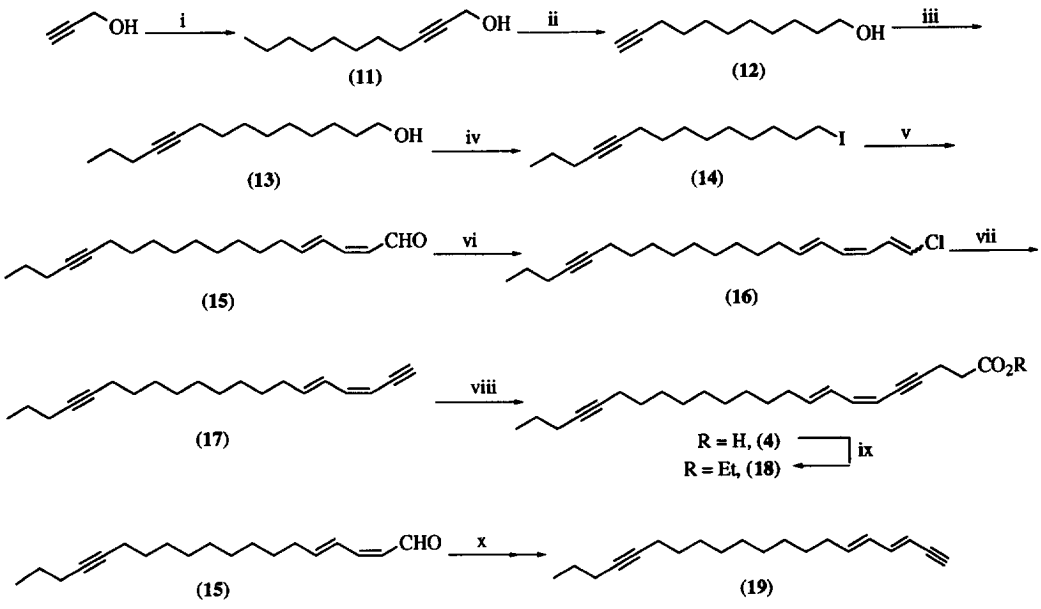
We next investigated procedures for effecting the alkyne-propionic acid homologation required for the synthesis of Carduusyne A (Scheme 2). Attempts to trap the acetylide derived from (**6a**) *in situ* with ethyl acrylate or β–propiolactone[12] were unsuccessful. We eventually found that the required homologation to give (**10**) could be achieved in reasonable yield commencing from purified alkyne (**7a**). Thus, deprotonation of (**7a**) using n-butyllithium, followed by sequential addition of dimethylaluminium chloride and β–propiolactone,[12] gave acid (**10**) as a single isomer (^{1}H-NMR: $J_{6,7}$ 10.0, $J_{8,9}$ 15.0 Hz) in 62% isolated yield.

Scheme 2



Having established a viable procedure for the preparation of the Carduusyne model compound (**10**), we investigated the application of this methodology to Carduusyne A itself (Scheme 3).

Scheme 3



Reagents and Conditions

(i) $LiNH_2/NH_3$, 1-bromooctane (41%); (ii) Li, 1,3-diaminopropane, $KOBu^t$ (36%);
(iii) $LiNH_2/NH_3$, 1-bromopropane (73%); (iv) Ph_3P, imidazole, I_2, CH_2Cl_2 (98%);
(v) ^tBuLi (2eq.), Et_2O, -78°C then pyrylium tetrafluoroborate (0.25eq.), Et_2O (85%);
(vi) Ph_3P=CHCl, THF, 0°C (92%); (vii) MeLi (3eq.), THF, 0°C (75%);
(viii) ^nBuLi, Me_2AlCl, β-propiolactone, toluene (20%; 98% based on recovered starting material);
(ix) $(COCl)_2$, DMF, CH_2Cl_2 then EtOH (99%);
(x) conc. HCl, $CHCl_3$-EtOH then (vi) then (vii) (52% overall yield).

Standard acetylene chemistry[13] was employed to convert propargyl alcohol into the homologated alcohol (**13**) via intermediates (**11**) and (**12**). Conversion[14] to iodide (**14**) followed by lithiation[15] and addition to pyrylium tetrafluoroborate gave dienal (**15**) in an optimised 85% yield. The use of diethyl ether as solvent and excess iodide were found to be necessary to prevent Wurtz-type couplings.[15]

Dienal (**15**) was efficiently converted into dienyne (**17**) *via* vinyl chloride (**16**) using the methodology described above. In order to ensure that isomerisation had not occurred during this process aldehyde (**15**) was isomerised to its *E,E*-isomer and then homologated to give the *E,E*-dienyne (**19**). The NMR data for (**17**) and (**19**) were distinctive and completely consistent with the assigned structures.[16] β–Propiolactone homologation of the *Z,E*-dienyne (**17**) afforded Carduusyne A (**4**) in low unoptimised yield (but with efficient recovery of unreacted starting material) which was efficiently converted into the corresponding ethyl ester (**18**) for characterisation.[17] The spectroscopic data for Carduusyne A ethyl ester (**18**) were entirely consistent with the published data[6] and the assigned structure.

In conclusion, we believe the methodology described herein demonstrates an efficient new stereocontrolled route to conjugated dienynes which should prove to be useful for the synthesis of other natural product targets.

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References and Notes

1. For a review see Sonogashira, K. *Comprehensive Organic Synthesis,* Pergamon Press, Oxford, 1991 (Vol. 3, Ch. 2.4).
2. For lead references see Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.,* 1985, **64**, 44; Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.,* 1984, **106**, 3548; Crousse, B.; Alami, A.; Linstrumelle, G. *Tetrahedron Lett.,* 1995, **36**, 4245.
3. Furber, M.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. I*, 1989, 683; Belosludtsev, Y. Y.; Borer, B. C.; Taylor, R. J. K. *Synthesis,* 1991, 320.
4. Hemming, K.; Faria De Medeiros, E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. I,* 1995, 2385.
5. Borer, B. C.; Taylor, R. J. K. *J. Chem. Res.(S),* 1990, 162; Faria De Medeiros, E.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. I,* 1991, 2725; Borer, B. C.; Taylor, R. J. K. *Synlett,* 1992, 117; Hemming , K.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.,* 1993, 1409.
6. Barrow, R. A.; Capon, R. J. *Aust. J. Chem.,* 1994, **47**, 1901.
7. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.,* 1972, 3769.
8. Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.,* 1973, 1495; Miyano, S.; Izumi, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.,* 1978, 446; Mella, M.; Panza, L.; Ronchetti, F.; Toma, L. *Tetrahedron,* 1988, **44**, 1673.
9. Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis,* 1979, 502.
10. All new compounds were fully characterised by high field ^{1}H- and ^{13}C-NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.
11. Key ^{1}H- NMR data for 4*Z*, 6*E*-undecadien-2-ynoic acid (**9a**): δ_H (270MHz, CD_3OD) 5.51 (1H, d, *J* 10.5Hz, H4), 6.09 (1H, dt, *J* 15.0, 7.5Hz, H7), 6.61 (1H, dd appears as t, *J* 10.5, 10.5Hz, H5), 6.79 (1H, dd, *J* 15.0, 10.5Hz, H6).
12. Shinoda, M.; Iseki, K.; Oguri, T.; Hayashi, Y.; Yamada, S.; Shibasaki, M. *Tetrahedron Lett.,* 1986, **27**, 87.
13. Brandsma, L. *Preparative Acetylenic Chemistry,* 2nd Edition, Elsevier, New York, 1988; Abrams, S. R.; Shaw, A. C. *Org. Synth.,* 1987, **66**, 127.
14. Lange, G. L.; Gottardo, C. *Synth. Comm.,* 1990, **20**, 1473.
15. Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.,* 1990, **55**, 5404; Negishi, E.; Swanson , D. R.; Rousset, C. J. *J. Org. Chem.,* 1990, **55**, 5406.
16. Key NMR data for 3*Z*, 5*E*-eicosadien-1,16-diyne (**17**): δ_H (270MHz, $CDCl_3$) 3.22 (1H, d, *J* 2.5Hz, H1), 5.30 (1H, dd, *J* 10.5, 2.5Hz, H3), 5.91 (1H, dt, *J* 15.0, 7.5Hz, H6), 6.43 (1H, dd appears as t, *J* 11.0 10.5Hz, H4), 6.60 (1H, ddd, *J* 15.0, 11.0, 1.0Hz, H5); δ_C (67.8MHz, $CDCl_3$) 81.0 (C2), 82.5 (C1), 105.5 (C3), 127.5 (C5), 140.0 (C6), 142.4 (C4).
3*E*, 5*E*-isomer (**19**): δ_H (270MHz, $CDCl_3$) 2.96 (1H, d, *J* 2.5Hz, H1), 5.47 (1H, dd, *J* 15.5, 2.5Hz, H3), 5.84 (1H, dt, *J* 15.0, 7.0Hz, H6), 6.09 (1H, dd, *J* 15.0, 10.5Hz, H5), 6.65 (1H, dd, *J* 15.5, 10.5Hz, H4); δ_C (67.8MHz, $CDCl_3$) 78.6 (C1), 83.1 (C2), 107.4 (C3), 129.3 (C5), 139.0 (C6), 143.9 (C4).
17. Data for synthetic Carduusyne A ethyl ester (**18**): δ_H (500MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.0Hz, $(H23)_3$), 0.98 (3H, t, *J* 7.0Hz, $(H2')_3$), 1.22-1.57 (16H, m, $(H11\text{-}H17)_2$, $(H22)_2$), 2.11-2.18 (6H, m, $(H10)_2$, $(H18)_2$, $(H21)_2$), 2.59 (2H, ddd, *J* 8.0, 7.5, 1.0Hz, $(H2)_2$), 2.70 (2H, br ddd, *J* 8.0, 7.5, 2.0Hz, $(H3)_2$), 4.18 (2H, q, *J* 7.0Hz, $(H1')_2$), 5.28 (1H, br d, *J* 10.5 Hz, H6), 5.85 (1H, dt, *J* 15.0, 7.5Hz, H9), 6.29 (1H, dd appears as t, *J* 11.0, 10.5Hz, H7), 6.53 (1H, br ddd, *J* 15.0, 11.0, 1.0Hz, H8); δ_C (125.8MHz, $CDCl_3$) 14.1 (C23), 14.2 (C2'), 15.7 (C3), 18.8 (C18/21), 22.6 (C22), 28.8, 28.9, 29.1, 29.2, 29.3, 29.4, 31.9 (C11-C17), 32.9 (C10), 33.8 (C2), 60.6 (C1'), 78.4 (C5), 80.0, 80.4 (C19/20), 93.6 (C4), 106.9 (C6), 127.7 (C8), 138.6 (C9), 139.8 (C7), 171.9 (C1); R_f 0.51 (light petroleum:diethyl ether, 5:1); ν_{max} 2927, 2854, 2249, 1735, 1639, 1463, 1377, 1261, 1097, 1070, 1037, 1014, 908 cm^{-1}; λ_{max} 269nm (ε 31200); HRCI: Found: MH^+, 371.2943. $C_{25}H_{39}O_2$ requires 371.2950 (2 ppm error).

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