Pergamon

Tetrahedron Letters, Vol. 37, No. 11, pp. 1751-1754, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00167-0

An Intramolecular Radical Approach To Angular Electrophores In Polycyclic Systems

Phillip A. Zoretic* and Yongzheng Zhang

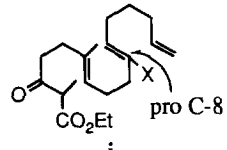
Department of Chemistry, East Carolina University, Greenville, NC 27858

Anthony A. Ribeiro

Duke NMR Spectroscopy Center, Department of Radiology, Duke University Medical Center, Durham, NC 27710

Abstract: The introduction of an angular C-8 cyano group in polycyclic system **9** has been realized *via* a stereoselective oxidative radical cyclization of polyene **8** containing an α,β-unsaturated electrophore.

The recent use of radicals[1] in the construction of complex molecules has become increasingly evident, since the initial radical studies of Breslow[2] and Julia.[3] The use of radicals to form polycyclic systems in a cascade fashion coupled with the introduction of multi-chiral centers and diverse functionality in a predictable manner presents an intriguing approach to an array of natural products. Snider[4] has elegantly demonstrated that radical cyclization of a β-keto ester polyene with Mn(III) in tandem with Cu(II) can be used as a stereoselective entry to *trans*-decalins. Recently we have demonstrated that intramolecular oxidative free-radical cyclization of a given β-keto ester polyene can be utilized to stereoselectively introduce five,[5,6] six,[5,7] and seven[8] stereogenic centers, respectively, in a polycyclic system in moderate yields. As an extension of these studies we were interested in determining if an electrophilic center could be introduced at a pro C-8 angular position in polyene **i**, since such a strategy would allow a direct entry to a variety of natural products containing a C-8



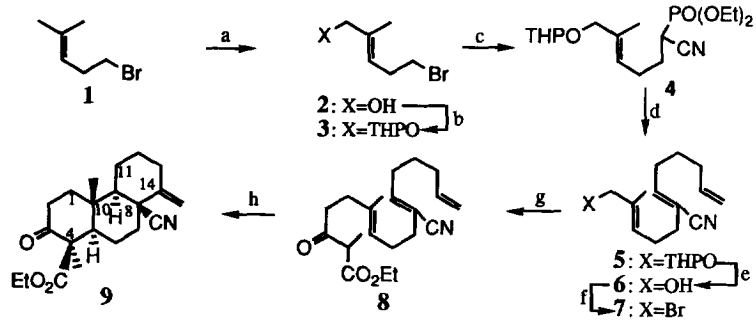
i

angular functional group. Secondly we were interested in determining what effect the incipient electrophilic radical would have on yields, since it was anticipated that the generation of such a radical in the cascade cyclization would lower the overall energy of the process and hence lead to a higher

yield of tricyclic product. Herein we wish to communicate the stereoselective synthesis of **9** and the ramifications of this initial oxidative radical cyclization study.

To introduce a C-8 angular electrophore in a given polycyclic system and to achieve a more efficient cyclization process, it was reasoned that both objectives could be met by cyclization of triene **8** containing a Z-trisubstituted $\Delta^{10,11}$-double bond. A stereoselective synthesis of targeted triene **8** was realized as detailed in Scheme I. Selective allylic oxidation[9] of homoallyl bromide **1**[10] afforded alcohol **2** in 44% yield, after chromatography. Reaction of **2** with dihydropyran in the presence of *p*-TsOH•H_2O yielded **3** (93%). Subsequent alkylation of sodio diethyl cyanomethylphosphonate with bromide **3** gave the cyanophosphonate ester **4** (62%). Introduction of the desired Z-trisubstituted $\Delta^{6,7}$-double bond in **5** was realized *via* a Horner-Emmons reaction using the conditions developed by Takayanagi.[11] Thus deprotonation of **4** with $KN(SiMe_3)_2$ in $PhCH_3$ at -78 °C followed by reaction of the potassium salt of **4** with 5-hexenal afforded an 89:11 mixture of 2E, 6Z-**5** and the corresponding 2E, 6E isomer. Chromatography on silica gel gave pure **5** (80%) and a 5% mixture of the 2E, 6E-isomer

Scheme I



[a] SeO_2, *t*-BuOOH; [b] Dihydropyran, *p*-TsOH•H_2O; [c] $(EtO)_2P(O)CH(Na)CN$; [d] $KN(SiMe_3)_2$, -78°C, then CH_2=$CH(CH_2)_3CHO$, -78°C (4h)->rt, overnight; [e] MeOH, *p*-TsOH•H_2O; [f] CBr_4, Ph_3P, CH_2Cl_2, rt, 1h; [g] $LiCH_2C(O)CMe(Na)CO_2Et$, 0°C, THF, 2h; then aq. HCl; [h] $Mn(OAc)_3$•$2H_2O$, $Cu(OAc)_2$•H_2O, HOAc, Ar.

and **5**. Cleavage of the THP protecting group in **5** with MeOH in the presence of *p*-TsOH•H_2O gave alcohol **6** (90%)[12] which upon treatment with CBr_4 and Ph_3P[13] afforded bromide **7** (86%). Alkylation of the dianion[14] of ethyl 2-methylacetoacetate (inverse addition) with **7** yielded the desired keto ester **8** (64%). Subsequent oxidative free-radical cyclization of **8**,[15] as a 0.1M solution in deaerated HOAc, with a 2:1 molar ratio of $Mn(OAc)_3$•$2H_2O$[16] and $Cu(OAc)_2$•H_2O gave cleanly and stereoselectively tricyclic keto ester **9** (mp 138-139 °C) in 60% yield, after chromatography. A series of 2D COSY, RELAY, TOCSY, HMQC, HMBC, and 1D APT NMR studies was used to fully identify each proton and carbon-thirteen resonance in **9**.[17] The A/B and B/C ring juncture stereochemistry shown in **9** is

consistent with the following observations. The large deshielding effect of the C-10 methyl group (1.28 δ) in **9** compared to the C-10 methyl shift (1.02 δ) in the analog[6] possessing a C-8 methyl group is consistent with the C-10 methyl group being 1,3-diaxially disposed to the nitrile and in its deshielding cone. It was also noted in the ^{1}H NMR spectrum that the C-9 methine proton appeared as a doublet of doublets with coupling constants of 2.6 and 12.2 Hz. These coupling constants are consistent with the trans B/C ring juncture stereochemistry depicted in **9** and are also in agreement with the values observed for the C-9 axial proton (0.89 δ, J=3 and 12.0 Hz) in the analog[6] possessing a C-8 methyl group.

The incorporation of an α,β-unsaturated nitrile in the polyene and the generation of the incipient electrophilic radical in **i** (X=CN) as opposed to a nucleophilic radical (X=CH_3)[6] has a pronounced effect on the yield increasing it by approximately 20%. This can be rationalized by assuming that the nitrile should facilitate both the second and third cyclizations. The second cyclization involves the addition of a nucleophilic alkyl radical to an electron deficient unsaturated nitrile while the third cyclization now involves the addition of an electrophilic radical, which can not be oxidized by Mn(III) or Cu(II), to a nucleophilic alkene.

A stereoselective intramolecular radical cascade cyclization strategy has been realized as an effective method of introducing an angular electrophore in polycyclic systems. Since the tether of the polyene can readily be modified by varying the aldehyde component in the Horner-Emmons reaction, a direct stereoselective entry to highly oxygenated[18] spongians possessing a C-8 hydroxymethyl group should be plausible. This type of strategy should also lend itself to the development of a reasonable radical cascade approach to steroids *via* decarbonylation of a C-8 aldehydeo or carboxyl group in an appropriately derived tetracyclic system.

Acknowledgement: We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and one of us (Y. Z.) would like to thank the Burroughs Wellcome Foundation for a research fellowship.

References and Notes

1. (a). Geise, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford and New York, **1986**; (b). Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541; (c). Curran, D. P. *Synthesis* **1988**, 417 and 489; (d). Surzur, J.-M.; Bertrand, M. P. *Pure Appl. Chem.* **1988**, *60*, 1659; (e). Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237; (f). Porter, N. A.; Giese, B.; Curran, D. P. *Acc. of Chem. Res.* **1991**, *24*, 296; (g). RajanBabu, T. V. *ibid.* **1991**, *24*, 139; (h). Melikyan, G. G. *Synthesis* **1993**, 833; (i). Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.

2. Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett.* **1968**, 1837; and references within.
3. Lallemand, J. Y.; Julia, M.; Mansuy, D. *Tetrahedron Lett.* **1973**, 4461.
4. Snider, B. B.; Mohan, R.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841.
5. Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z.; Ribeiro, A. A. *J. Org. Chem.* in press.
6. Zoretic, P. A.; Shen, Z.; Wang, M.; Ribeiro, A. A. *Tetrahedron Lett.* **1995**, *36*, 2925.
7. Zoretic, P. A.; Zhang, Y; Ribeiro, A. A. *Tetrahedron Lett.* **1995**, *36*, 2929.
8. Zoretic, P. A.; Weng, Y; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1991**, *32* , 4819.
9. Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
10. Julia, M.; Julia, S.; Guegan, R. *Bull. Soc. Chim. Fr.* **1960**, 1072.
11. Takayanagi, H. *Tetrahedron Lett.* **1994**, *35*, 1581.
12. All new compounds gave satisfactory spectral and analytical data.
13. Hagashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749; and references within.
14. Huckin, S. N.; Weiler, L. J. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
15. ^{1}H NMR(200 MHz, $CDCl_3$, δ) for other compounds in this work are: **2** 5.44(m, 1H), 4.02(s, 2H), 3.39(t, 2H), 1.68(s, 3H); **3** 5.45(m, 1H), 4.61(br t, 1H), 4.12(d, 1H, J=12 Hz), 3.87(d, 1H, J=12Hz), 3.37(t, 2H), 1.68(s, 3H); **4** 5.38(m, 1H), 2.94(dt, 1H, J=7.8, 23.0 Hz), 1.71(s, 3H), 1.39(t, 6H, J=7.1 Hz); **5** 6.13(t, 1H, J=7.6 Hz), 5.79(m,1H), 5.36(m, 1H), 4.94-5.13(m, 2H), 4.11(d, 1H, J=11.9 Hz), 3.84(d, 1H, J=11.8 Hz), 1.67(s, 3H); **6** 6.15(t, 1H, J=7.7 Hz), 5.80(m, 1H), 5.37(m, 1H), 4.00(br s, 2H), 1.68(s, 3H); **7** 6.14(t, 1H, J=7.7 Hz), 3.95(s, 2H), 1.78(s, 3H); **8** 6.12(t, 1H, J=7.5Hz), 4.19(q, 2H), 3.51(q, 1H), 1.33(d, J=7.2 Hz) and 1.27(t, J=7.1 Hz)[6H].
16. Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759.
17. The ^{1}H NMR(500 MHz, $CDCl_3$, δ) data for **9**: 4.92(d, 1H, J=1.6 Hz), 4.84(s, 1H), 4.17(m, 2H), 2.99(6 line ddd, 1H, H_{2ax}, J=6.4, 14.8 Hz), 2.49(m, 1H, H_{13ax}), 2.41(partially resolved 8 line ddd, H_{2eq}, J=2.6, 4.7, 15.0 Hz) and 2.29-2.40(m, H_{6ax}, H_{13eq}, H_{7eq})[4H], 2.12(ddd ,1H, H_{1eq}, J=2.5, 6.4, 13.2 Hz), 2.05(apparent dq, 1H, H_{6eq}, J=3.1, 14.5 Hz), 1.97(m, 1H, H_{12eq}), 1.86(m, 1H, H_{11eq}), 1.70(partially resolved 8 line ddd, H_{11ax}, J=3.6, 13.6 Hz) and 1.66(partially resolved 6 line ddd, H_{7ax}, J=3.6, 13.9 Hz)[2H], 1.38(s, 3H, C4-Me), 1.29(t, J=7.1 Hz), 1.28(s, C10-Me) and 1.23-1.31(H_{1ax}, H_{5ax}, H_{12ax})[9H], 0.99(dd, 1H, H_{9ax}, J=2.6, 12.2 Hz); ^{13}C NMR(500 MHz, $CDCl_3$, δ) 207.7(C3), 173.3(ester CO), 148.0(C14), 122.3(CN), 109.3(exo CH_2), 61.4(CH_2O), 57.3(C4), 57.1(C5), 56.9(C9), 43.0(C8), 39.8(C1), 38.4(C10), 36.4(C2), 35.0(C7), 33.7(C13), 27.5(C12), 23.9(C11), 21.3(C6), 20.9(C4-Me), 13.9(C10-Me), 12.6(ethyl CH_3).
18. Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Noack, K.; Oberhansli, W. E.; Schonholzer, P. *Aust. J. Chem.* **1979**, *32*, 867; Gunasekera, S. P.; Schmitz, F. J. *J. Org. Chem.* **1990**, *56*, 1250.

(*Received in USA* 11 *December* 1995; *revised* 16 *January* 1996; *accepted* 18 *January* 1996)