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A MILD FOUR-CARBON HOMOLOGATION OF ALDEHYDES TO E,E-DIENAMINES!

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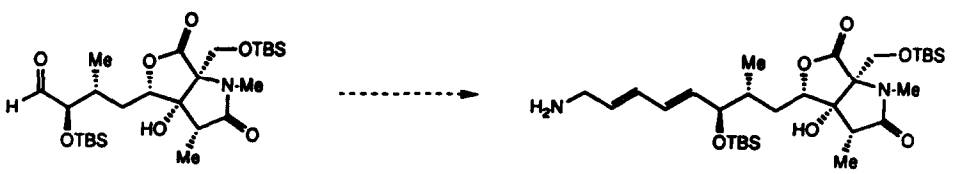
SUMMARY: The four-carbon homologation of aldehydes to E,E-dienamines can be achieved efficiently under mild conditions by iodomethylenation with $CrCl_2$-CHI_3, with subsequent Pd-catalyzed coupling to the vinylstannane **4** followed by mild cleavage of the FMOC group.

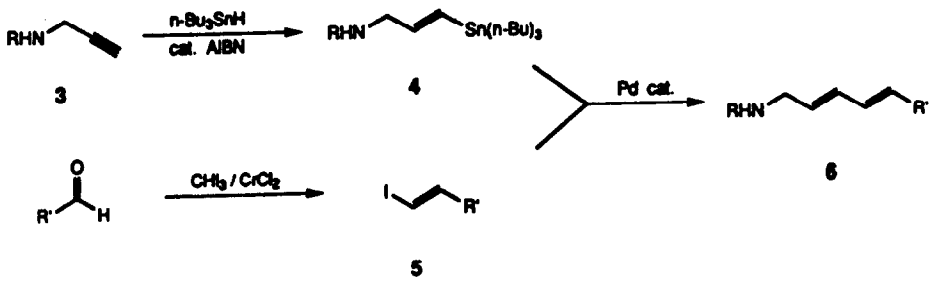
In the course of our current studies toward the total synthesis of the antitumor antibiotic neooxazolomycin,[3] we required a mild and efficient method for the stereocontrolled four-carbon homologation of a sensitive aldehyde (**1**) to the corresponding dienamine (**2**).



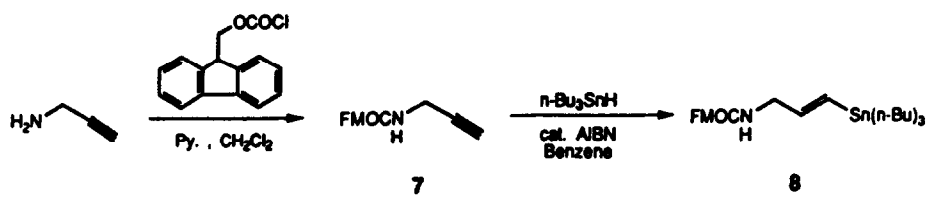
1 **2**

Although various sequences to achieve the desired transformation are suggested by the literature,[4] all are multistep and require vigorous conditions for final deprotection of the amine group. Since these features were undesirable for the sensitive polyfunctional system to be employed, we have developed a new, gentle and convenient general method to achieve the requisite transformation. Our plan (Scheme 1) was to convert a suitably protected propargylamine (**3**) to an E-vinylstannane (**4**) by hydrostannylation. Palladium-catalyzed cross coupling[5] of this vinylstannane with an E-iodoalkene (**5**), easily prepared from any aldehyde using Takai's CHI_3-$CrCl_2$ system,[6] would afford the protected E,E-dienamine **6** under neutral conditions. Essential to this approach was the selection of an amine protecting group that was compatible with the generation of E-vinylstannane **4**, with the subsequent Pd coupling, and which could be removed in high yield under very mild conditions.

Scheme 1

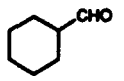
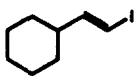
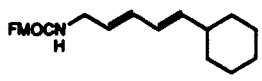
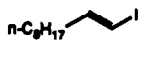
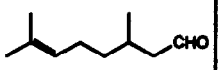
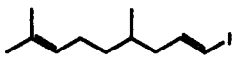
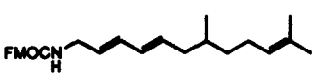
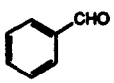
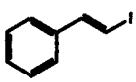
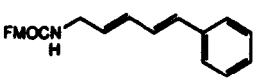
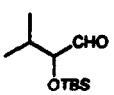
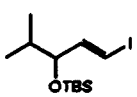
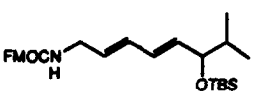


After considerable experimentation we chose the fluorenylmethoxycarbonyl (FMOC) protecting group developed by Carpino.[7] Propargylamine was reacted with FMOC-chloride (Fluka) and pyridine (1 equiv each, CH_2Cl_2, 0° to 20°, 40 min) to give a 95% yield of the crystalline FMOC-amine 7, mp 126-127°.[8] The triple bond was hydrostannylated (1.0 equiv n-Bu_3SnH, cat AIBN, C_6H_6 under argon, reflux, 5h)[9] to give, after silica gel chromatography, a 55% yield of the E-vinylstannane 8.[10]

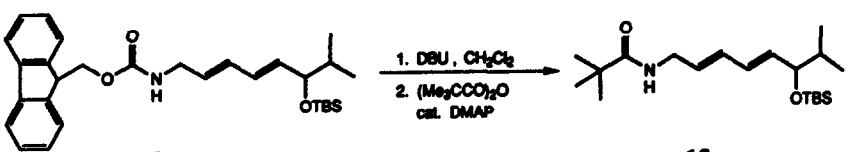


As shown in Table 1,[11] the vinylstannane 8 undergoes smooth coupling (5 mol % $PdCl_2(MeCN)_2$, DMF, 20°, 24 h, argon atm.) with a variety of 1-iodoalkenes (prepared as reported by Takai from the listed aldehydes)[6] to afford FMOC-protected dienamines in good yields. A minor amount of kinetic stereoselection from E/Z-iodoalkene mixtures is observed (column B vs C), and in each case the pure E,E-diene product was readily isolated by silica gel preparative TLC. A simple model for aldehyde 1, namely entry 5 of Table1,[12] is converted by this method in 55% overall yield to the corresponding E,E-FMOC-dienamine 9 with >98% stereoselectivity.

Table 1

Entry No.	Aldehyde (A)	Iodoalkene, yd(E/Z) (B)	Dienamide, yd (E,E/E,Z) (C)
1		 78 % (89 : 11)[6]	 63 % (90 : 10)[7]
2	n-C_8H_{17}CHO	 82 % (83 : 17)[6]	 61 % (85 : 15)[7]
3		 84 % (82 : 18)[6]	 65 % (85 : 15)
4		 97% (95 : 5)[6]	 65 % (> 95 : 5)
5[12]		 65 % (99 : 1)	 84 % (> 99 : 1)[7]

To demonstrate the facile, one-pot deprotection-acylation sequence we envision for future coupling the amine and acid halves of neooxazolomycin, the FMOC-amine **9** was treated with DBU (2 equiv) in dry CH_2Cl_2 at 20° for one hour. After TLC showed complete deprotection, 1.2 equiv of pivalic anhydride and DMAP catalyst were added. We thereby obtained a 95% overall yield of crystalline pivalamide **10**, mp 68-70°, after workup and silica gel chromatography.[13]



9 **10**

The use of the Takai iodomethylenation, followed by Pd coupling with an FMOC-protected E-vinylstannane unit (**4**) thus comprises an exceptionally mild and highly stereoselective C_4 elaboration of even sensitive aldehydes to the E,E-dienamines of the type required for the construction of neooxazolomycin.[14]

Acknowledgments Partial support of this research by grant CA-18846, awarded by the National Cancer Institute, is gratefully acknowledged.

REFERENCES AND NOTES

1. Dedicated to the memory of Professor John K. Stille, deceased July 19, 1989.

2. Smith Kline and French Predoctoral Fellow, 1988-89.

3. For earlier work toward this target, see: (a) Kende, A. S.; DeVita, R. J. Tetrahedron Lett. **1988**, 29, 2521 (b) Kende, A. S.; Kawamura, K. Tetrahedron Lett. **1989**, in press.

4. For some examples of allylic amine syntheses from aldehydes or aldehyde derived precursors see: (a) Connell, R.D.; Rein, T.; Akermark, B.; Helquist, P. J. Org. Chem. **1988**, 53, 3845; (b) Ishii, T.; Kawamura, N.; Matsubara, S.; Utimoto, K.; Kozima, S.; Hitomi, T. J. Org. Chem. **1987**, 52, 4418; (c) Nikaido, M.; Aslanian, R.; Scavo, F.; Helquist, P.; Akermark, B.; Bäckvall, J.-E. J. Org. Chem. **1984**, 49, 4740; (d) Meyers, A.I.; Lawson, J.P.; Carver, D.R. J. Org. Chem. **1981**, 46, 3119; (e) Cavalla, D.; Warren, S. Tetrahedron Lett. **1982**, 23, 4505, and references contained therein.

5. Stille, J.K.; Groh, B.L. J. Am. Chem. Soc. **1987**, 109, 813.

6. Takai, K.; Nitta, K.; Utimoto, K. J. Am. Chem. Soc. **1986**, 108, 7408.

7. Carpino , L.A.; Han, G.Y. J. Org. Chem. **1972**, 37, 3404. For a review see: Atherton, E.; Sheppard, R.C. in "The Peptides: Analysis, Synthesis and Biology", Vol. 9 S. Udenfriend and J. Meienhofer, Eds., **1987**, Academic Press (N.Y., N.Y.), pp 1-38.

8. Compound 7: Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45. Found: C, 78.02; H, 5.50.

9. Stille, J. K. Angew. Chem. Int. Ed. Eng. **1986**, 25, 508 and references therein.

10. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.78 (2H, d), 7.63 (2H, d), 7.42 (2H, t), 7.33 (2H, t), 6.16 (1H, d, J = 18.8 Hz), 6.00 (1H, dt), 4.86 (1H, br s), 4.44 (2H, d), 4.25 (1 H, t), 3.90 (2H, t), 1.48 (6H, m), 0.90 (15 H, m). Anal. Calcd. for $C_{30}H_{43}NO_2S$: C, 63.34 ; H, 7.63. Found: C, 63.65 ; H, 7.65.

11. All iodoalkenes and FMOC-amines of Table I gave ^{1}H NMR spectra in accord with the assigned structures. Selected data for the FMOC-amines are given below. Entry 1 C: mp 120-122°, Found: C, 80.30; H, 7.52. Entry 2C: mp 88-90°, Found: C, 80.61; H, 8.35. Entry 3C: mp 62-64°, Found: C, 81.16; H, 8.21. Entry 4C: mp 136-138°. Entry 5C (= 9), mp 60-62°, Found: C, 73.55; H, 8.44; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.78 (2H, d, J = 7.5 Hz), 7.62 (2H, d, J = 7.4), 7.42 (2H, t), 7.33 (2H, t), 6.14 (2H, m), 5.65 (2H, m), 4.83 (1H, br s), 4.44 (2H, d, J = 6.8), 3.88 (3H, m), 1.68 (1H, m), 0.92 (9H, s), 0.87 (6H, t), 0.05 (3H, s), 0.01 (3H, s).

12. Aldehyde entry 5A of Table 1 was prepared from isobutyraldehyde by: (a) reaction with excess vinyl MgBr (b) silylation with TBSCl/imidazole in DMF and (c) O_3 with DMS workup.

13. Amide **10**: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.15 (2H, m); 5.66 (3H, m); 3.89 (3H, m), 1.66 (1H, m), 1.22 (9H, s), 0.90 (9H, s), 0.86 (6H, t), 0.04 (3H, s), 0.00 (3H, s). Anal. Calcd. for $C_{20}H_{39}NO_2Si$: C, 67.93 H, 11.12. Found: C, 68.16; H, 11.16.

14. For the use of this methodology on intermediates related to the "right half" of neooxazolomycin, see DeVita, R.J., Ph.D. Thesis, University of Rochester, Department of Chemistry, 1989.

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