Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4355-4358, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00933-7

Application of Ene-Like Reactions of Aldehydes with Vinyl Ethers: Facile Assembly of Benzazocenone Intermediates for Mitomycinoids

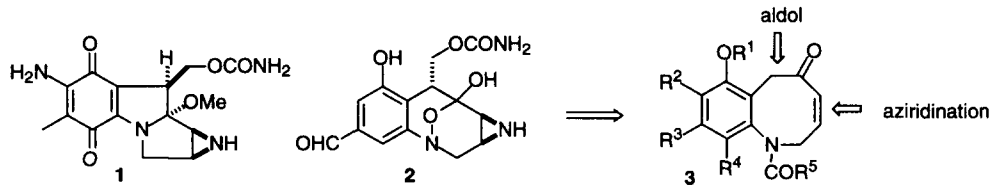
Marco A. Ciufolini,*[1] Mingying Chen, Dennis P. Lovett and Melissa V. Deaton

Department of Chemistry, MS 60, Rice University, 6100 Main St., Houston, Texas 77005-1892, U.S.A.

ABSTRACT: Benzazocenone intermediates for mitomycinoids are now available in only six steps. Key phases of this sequence include the ene-like reaction of 2-methoxypropene with a 2-azidophenyacetaldehyde and a novel heterocyclic ring formation/expansion reaction. © 1997 Elsevier Science Ltd.

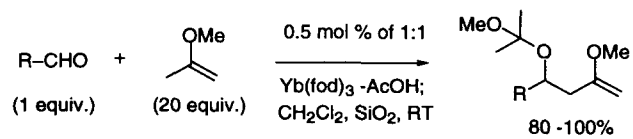
Mitomycinoids, e.g., mitomycin C, **1**, and FR900482, **2**, are potent antitumor agents that have elicited much attention from the synthetic community.[2] These molecules could be constructed starting from a benzazocenone of the type **3** (Scheme 1), and indeed, some especially successful syntheses of mitomycinoids proceed through similar 8-membered ring intermediates.[3] However, benzazocenones and related medium ring compounds are generally difficult to assemble. Recent progress in olefin metathesis chemistry has facilitated this task significantly.[4] In this Letter, we propose a practical alternative that relies on our ene-like reaction of ordinary

Scheme 1



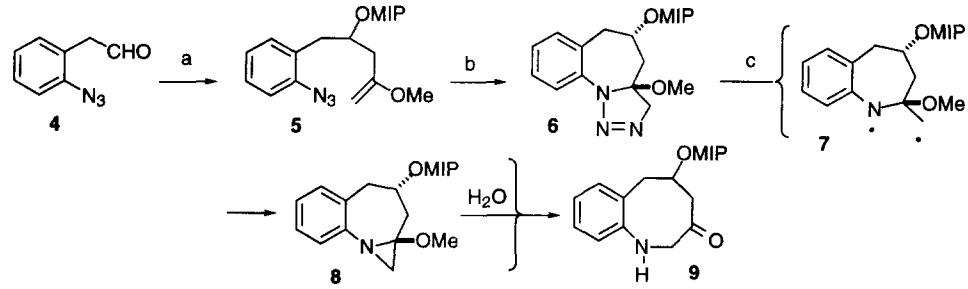
aldehydes with those vinyl ethers such as 2-methoxypropene (MP), that display the oxygen atom at the central carbon of an allylic system.[5] This process,[6] outlined in Scheme 2, is efficient and economical; it requires only 0.5 mol% or less of a catalyst consisting of the 1:1 complex of $Yb(fod)_3$ and acetic acid, it occurs at room temperature it requires no drastic measures to exclude air or moisture, it affords end-products in nearly quantitative yield and in high purity, and it offers much strategic and tactical opportunity.[7]

Scheme 2



Central to the success of our plan was the ability of 1,3-dipolar functionality, e.g., an azide strategically placed within the substrate aldehyde, to intercept the vinyl ether subunit of the ene product as a prelude to a novel photochemical ring expansion. This is shown in Scheme 3. Ene-like reaction of 2-(2-azidophenyl)-acetaldehyde **4**[8] with MP furnished ene adduct **5** (MIP = 2-methoxyisopropyl; cf. Scheme 2), cyclization of which to triazoline **6** was best effected in refluxing toluene (55% chromat. yield from **4**). Irradiation of a solution of **6** in moist THF with UV light from a sunlamp (pyrex flask), and without the need for a sensitizer, promoted efficient conversion to benzazocenone **9** in 84% chromatographed yield. Only three steps are thus necessary to assemble **9** from readily available materials, thanks to synergy between our ene-like reaction and the photochemistry of Scheme 3.

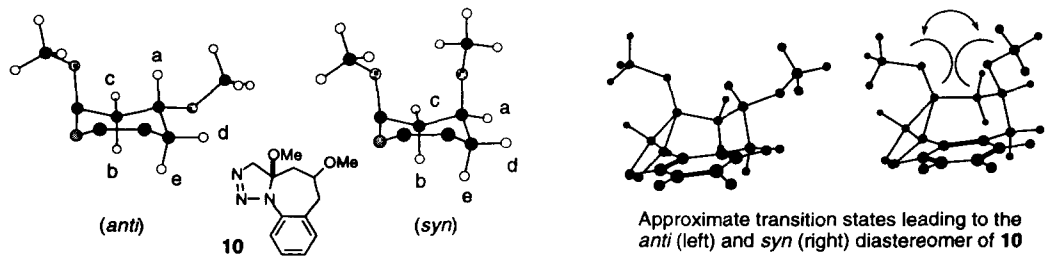
Scheme 3



(a) MP (20 equiv.), CH_2Cl_2, 0.5 mol% of 1:1 Yb(fod)$_3$-AcOH, RT, 20 h; (b) Toluene, reflux, cat. K_2CO_3, 14 h, 55 % chrom. a-b; (c) hv (Sylvania 275 W sunlamp), cat. K_2CO_3, moist THF, 32 h, 78 - 84%.

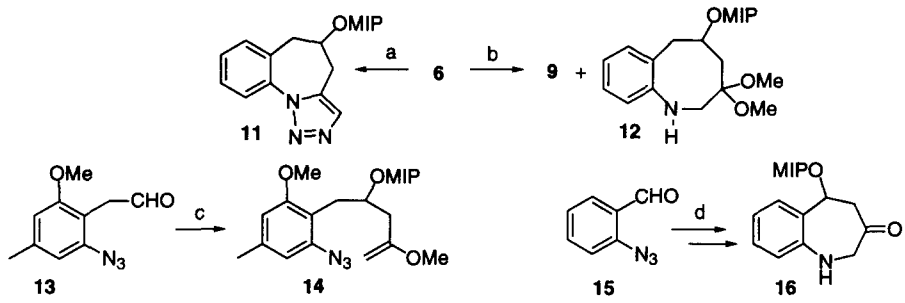
Various aspects of Scheme 3 deserve further comment. First, compound **6** emerged as a 7:1 mixture of isomers. The major one, m.p. 88-90° C (recr'd. EtOAc/hexanes), is believed to be the *anti* diastereomer (shown above), due to large couplings (11 and 8 Hz) between the H on the OMIP - bearing C atom and two neighboring H's. Scheme 4 shows the 7-membered ring portion of the MM+ optimized structures of the *anti* and *syn* diastereomers of **10**, an analog of **6** wherein the MIP unit is approximated by a computationally more tractable methyl group (the rest of the molecules is invisible for clarity). Only the *anti* isomer displays sufficiently large dihedral angles between proton **a** and neighboring hydrogens **b** and **e** to permit 8-11 Hz couplings. Moreover, approximate transitions states (TS) for the dipolar cycloaddition leading to the isomeric triazolines were estimated by fixing the distance between the terminal N atoms of the azide and the olefinic C atoms of the vinyl ether to 2.4 Å. It appears that the approximate TS leading to the *syn* isomer is affected by a severe nonbonding interaction between the oxygen atoms on the vinyl ether and the OMe / OMIP unit. This interaction is absent in the TS

Scheme 4



Approximate transition states leading to the *anti* (left) and *syn* (right) diastereomer of **10**

Scheme 5

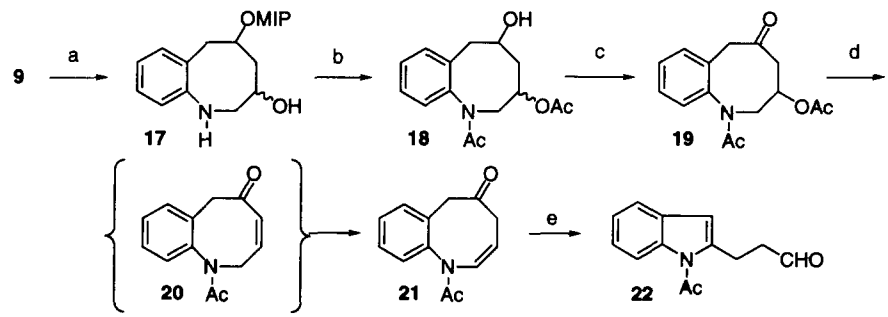


(a) cat. H^+; (b) hv (sunlamp), cat. K_2CO_3, PhH, MeOH; (c) MP, CH_2Cl_2, 0.005 equiv. 1:1 Yb(fod)$_3$: AcOH, r.t., 95%; (d) cf. Scheme 3; 86% overall.

leading to the *anti* isomer, which therefore should form preferentially.[9] Second, the triazoline was prone to undergo loss of MeOH with consequent aromatization to triazole **11** (Scheme 5). This triazole resisted photochemical deazoniation, but fortunately aromatization of **6** was easily suppressed by handling it always in the presence of some solid K_2CO_3. Third, conversion of **6** to **9** probably starts with deazoniation (cf. Scheme 3). The resulting 1,3-diradical **7** would be expected to cyclize to methoxyaziridine **8**. Rapid hydrolysis of this fragile, strained material would ensue in the presence of water. In support of this mechanistic picture, irradiation of **6** in Ph / MeOH led to acetal **12**, in addition to **9**, presumably through capture of **8** by MeOH. Fourth, the ene step is not particularly sensitive to additional substituents *ortho* to the reaction site. This is underscored by the successful formation of adduct **14** from aldehyde **13**, which displays a substitution pattern more closely resembling **2**. Finally, the tandem dipolar cycloaddition-photochemical ring expansion of Scheme 3 succeeds also with other substrates. To illustrate, 2-azidobenzaldehyde, **15**,[8b] was readily advanced to benzazepinone **16**.

Experiments directed toward the conversion of **9** to an azocenone of the type **3** revealed an interesting property of the final heterocycle. Briefly, $NaBH_4$ reduction of **9**, acetylation of the mixture of diastereomers of **17** and catalytic TPAP oxidation[10] of the free carbinol in **18** (the MIP group was cleaved during acidic workup of

Scheme 6



(a) $NaBH_4$, EtOH, –20°C; (b) Ac_2O, pyr, acid workup (– MIP), 65 % a-b; (c) cat. TPAP, NMO, CH_2Cl_2; (d) DBU, 78 % chrom.; (e) H_3O^+.

the acetylation reaction) produced acetoxyketone **19** (Scheme 6). This material was rather resistant to β-elimination to **20**. Elimination could be forced by exposure of **19** to DBU at room temperature; however, rapid deconjugation of the presumed enone intermediate **20** occurred under these conditions, resulting in the ultimate formation of enamide **21**. The structure of **21** rests on extensive 2D HMBC studies[11] and on its chemical conversion into indole **22**. It seems likely that a similar elimination reaction should produce the desired regiochemical outcome if the ketone in **19** were not expressed,[12] since this would deny the intermediate olefin a pathway for rearrangement. We hope to parlay the favorable premises detailed in this paper into a synthesis of at least some mitomycinoids. Developments in this area will be reported in due course.[13]

Acknowledgment. We thank NIH (CA-55268), NSF (CHE 95-26183), the Robert A. Welch Foundation (C-1007), and the Alfred P. Sloan Foundation, for support of our research.

References and Footnotes

1. Fellow of the Alfred P. Sloan Foundation.
2. Reviews: (a) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549; (b) Remers, W. A.; Dorr, R. T., in: *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley & Sons: New York, NY, 1988; vol. 6, ch. 1. Recent syntheses: (c) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881; (d) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722.
3. Ref. 2a-b as well as: (a) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1992**, *114*, 383; (b) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S *Tetrahedron Lett.* **1996**, *37*, 3471; (c) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3475; (d) Katoh, T.; Yoshino, T.; Nagata, Y.; Nakatani, S.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3479.
4. (a) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169; (b) Martin, S. F.; Chen, H. J.; Courtney, A. K.; Liao, Y. S.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251.
5. Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409.
6. Ciufolini, M. A., in: *Advances in Heterocyclic Natural Product Synthesis* ; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1996, vol. 3, ch. 1.
7. Ciufolini, M. A.; Deaton, M. V.; Zhu, S.; Chen, M. *Tetrahedron* **1997**, *53*, *In Press.*
8. a. Made from 2-(2-aminophenyl)-ethanol (Aldrich) by (i) diazotization/azidation; (ii) PCC oxidation (≈40%). Cf.: b. Ardakani, M. A.; Smalley, R. K.; Smith, R. H. *J. Chem. Soc., Perkin Trans. I* **1986**, 4139.
9. All calculations (MM+ force field) were carried out with the Hyperchem 4.0® package, by Hypercube, Inc..
10. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
11. We thank Drs. Lawrence Alemany and William Wilson for invaluable assistance with these measurements.
12. Related eliminations tend to occur away from heteroatoms, e.g.: Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.
13. All compounds were fully characterized (^{1}H, ^{13}C NMR; IR; low, high resolution MS). ^{1}H NMR data for representative compounds: **6** ^{1}H (C_6D_6) 7.82 (d, 1H, J = 7.8), 7.08-6.74 (m, 3H), 4.31 (dddd, 1H, J = 11.0, 7.7, 4.7, 3.4), 4.14 (d, 1H, J = 18.4), 3.48 (d, 1H, J = 18.4 Hz), 3.10 (s, 3H), 2.96 (m, 2H), 2.57 (dd, 1H, J = 13.3, 2.2), 2.46 (s, 3H), 1.60 (dd, 1H, J =11.0, 2.0), 1.53 (dd, 1H, J = 13.3, 11.0), 1.28 (s, 3H), 1.27 (s, 3H). **9** ^{1}H (C_6D_6) 6.99 (t, 1H, J =7.3), 6.94 (d, 1H, J = 7.9), 6.73 (t, 1H, 7.), 6.26 (d, 1H, J = 7.9), 4.13 (m, 1H), 3.43 (d, 1H, J = 18), 3.23 (d, 1H, J = 18.0), 3.12 (s, 3H), 3.01 (dd, 2H, J = 10.3, 4.2), 2.81 (dd, 2H, J = 4.2, 3.6), 1.23 (s, 6H). **21**: ^{1}H ($CDCl_3$) 7.45-7.20 (m, 5H), 5.02 (dt, 1H, J = 9.6, 5.3), 3.81 (d, 1H, J = 16.7), 3.58 (d, 1H, J = 16.7), 2.82 (dt, 1H, J = 13.8, 3.5), 2.55 (dd, 1H, J = 13.8, 9.8), 1.80 (s, 3H).

(*Received in USA* 15 *April* 1997; *revised* 7 *May* 1997; *accepted* 8 *May* 1997)